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Title: Extended and standard duration weight loss referrals for adults in primary care (WRAP): a pragmatic randomised controlled trial.

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Abstract: Background

There is good evidence that primary care referral to an open-group behavioural programme is an effective treatment for obesity, but little evidence on optimal treatment duration.

Methods

In this non-blinded parallel-group randomised controlled trial, we recruited participants (age ≥ 18 years, BMI ≥ 28 kg/m²) through 23 primary care practices in England. Participants were randomised using the study database in a 2:5:5 allocation to: brief weight loss intervention, a weight management programme (Weight Watchers®) for 12 weeks, or the same weight management programme for 52-weeks. We followed participants over two years. The primary outcome was weight at one year, analysed using mixed-effects models according to intention-to-treat principles adjusted for centre and baseline weight. In a hierarchical-closed-testing procedure we compared combined behavioural programme arms with brief intervention, then compared the 12-week and 52-week programmes. We conducted a within-trial cost-effectiveness analysis using person-level data and modelled outcomes over a 25-year horizon using microsimulation. Current Controlled Trials ISRCTN82857232.

Findings

Between 18th October 2012 and 10th February 2014, 1267 eligible participants were randomised to the brief intervention (211), 12-week programme (528) and 52-week programme (528). 823 (65%) completed an assessment at one year and 856 (68%) at two years. All participants were included in the analyses. At one year, mean weight change was -3.26 kg (brief intervention), -4.75 kg (12-week programme), and -6.76 kg (52-week programme). Participants in the behavioural programme lost more weight than those in the brief intervention [adjusted difference = -2.71 kg (95% CI -3.86, -1.55); $p < 0.0001$]. The 52-week programme was more effective than the 12-week programme [adjusted difference = -2.14 kg (95% CI -3.05, -1.22); $p < 0.0001$]. Differences between groups were still significant at two years. No adverse events related to the intervention were reported. Over two years, the incremental cost-effectiveness ratio (ICER; compared with brief intervention) was £159/kg lost for the 52-week programme and

£91/kg for the 12-week programme. Modelled over 25 years after baseline, the ICER for the 12-week programme was dominant compared with the brief intervention. The ICER for the 52-week programme was cost-effective compared with the brief intervention (£2498/QALY) and the 12-week programme (£3804/QALY).

Interpretation

For adults with overweight or obesity, referral to this open-group behavioural weight loss programme for at least 12 weeks is more effective than brief advice and self-help materials. A 52-week programme produces greater weight loss and other clinical benefits than a 12-week programme and, although it costs more, modelling suggests it is cost-effective in the longer term.

Dear Jennifer,

We thank the reviewers for their positive appraisal and the constructive comments on our manuscript. Below, please find a point by point response to the questions raised by the reviewers. In addition to the edits requested by the reviewers, we have made a number of small changes. These are listed at the end of the response to reviewers. We hope that you will agree that this response addresses the reviewers' comments and we thank you for your continued consideration of our manuscript.

Kind Regards

Amy

Response to the Reviewers.

Reviewer #5: The inclusion of the 24mo and economic data greatly alleviates my primary concerns with this paper. The inclusion of these data have greatly strengthened the conclusions.

p13 line 12 - "broadly generalizable" has been added to soften conclusions about sample representativeness. I feel as though clearer acknowledgement should be given about the high proportion of females. I appreciate that this is typical of weight management trials. However, in this section the authors refer to the "UK population" which is not 68% female.

We believe 'broadly generalizable' is an appropriate term here, as although the gender split is not representative of the UK population, we identified no interaction between gender and intervention on weight loss. We have added a caveat to P13 L13 to reiterate that there are still a lower proportion of males than is seen in the UK population.

The Table 4 heading needs to be adjusted to reflect presentation of 24mo data.
This table heading has been amended

Reviewer #7: The authors present findings from a randomised controlled trial comparing weight loss, other clinical and quality of life measures between participants referred to an extended weight loss programme and participants referred to a 12-week weight loss programme. Both arms are also compared with a brief intervention. The statistical analysis is thorough and appropriate and the authors have done a good job of addressing the reviewers' comments. However, there are still some questions that I think they should address in order to make the paper suitable for publication.

Major points

1. One issue that I don't think is sufficiently addressed in the manuscript is the fact that, by design, when outcomes are assessed at 12 and 24 months, the time lag from the end of the weight loss programme differs between the two weight management programmes (at the 12 month time point, the 12 week programme has finished 9 months earlier and the 52 week programme has just finished; at the 24 month time point, the 12 week programme has finished 21 months earlier and the 52 week programme has finished 12 months earlier). Did the authors ever consider having an outcome measurement at the same time lag from finishing the intervention and comparing results at this time point between the two arms? Obviously this can't be added now and may not make sense from a programmatic point of view, but it might be interesting to think about whether the effects of a longer-term intervention are sustained over a longer period of time (after the intervention has ended) compared to the longer-term effects of a shorter-term intervention. Related to this, in the

discussion the authors state "On average all groups regained some of the weight lost and at 2-years the difference in weight loss between the 12-week programme and the brief intervention was no longer significant, whereas the weight loss in the 52-week programme was significantly greater than both other groups." Relating to the point above that this could just be because those in the 12-week programme finished going to weight watchers longer ago than those in the 52 week programme, so this point could be mentioned.

As the reviewer notes, the trial was designed to compare the cost-effectiveness of different length interventions at pre-specified time points over a 2 year period. It would not make sense to have different lengths of follow up for the different interventions. In addition, changing the timing of assessments based on intervention length could introduce problems with variable attrition rates over time and differences between groups in age at follow up. This issue is highlighted when we consider the brief intervention. End of intervention for the brief intervention group would be the end of the baseline appointment.

2. *The secondary outcome "triglycerides" was not listed in the protocol as far as I can see. While "triglycerides" are not specified, they are encompassed in the more general term "lipid profile".*

3. *"Potential interactions between intervention effects and gender, educational qualification and income were examined, as a recent review highlighted the lack of evidence of this type of programme on socio-economic inequalities". I think it could be made even more clear that these subgroup analyses were not planned at the start of the study (they are not in the protocol) but were instead added later on as new research was published.*

We have moved the description of this analysis to a new paragraph to make clear its separation from the protocol-specified trial analysis and we have edited to be clear that this was a post-hoc analysis.

4. *Outcomes "self-reported quality of life (EQ5D-3L) and health resource use at 3, 12 and 24 months" are reported. I don't think it was clear in the protocol that these specific psychosocial and process measures would be included as outcomes (others are also listed but not mentioned in the manuscript, for example other psychosocial measures such as SRHI and VAS). It would be good if the authors could either mention these in the results of this paper or explain in a response why they're not included. Personally I think they don't have to be included in this paper as the protocol doesn't explicitly state that they will be, but it would be interesting to hear what the plans are.*

The psychosocial measures included in this trial were not designated as clinical outcomes. They were added to enable us to conduct future work on how baseline differences in these factors affect weight trajectories, how these factors change during and following a weight loss intervention, and how changes are associated with changes in weight. This is specified in the protocol. We have included self-reported quality of life and health resource use in this manuscript as these are relevant to the economic evaluation which was specified in the protocol.

5. *In the results, it is stated "There were no differences between intervention groups in the number of participants completing a 24-month assessment (p=0.21)." Please could the authors also include information on whether there were any differences at 12 months.*

There was a borderline statistical difference in attendance at 12 months. We have added this to the manuscript (P10. L12)

"Using Pearson's Chi-squared test, there was a borderline statistically significant association between the percentage of participants attending the 12-month appointment and intervention

group ($p=0.047$), though there was little evidence to suggest such an association for participants completing the 24-month assessment ($p=0.212$)."

6. *Reviewer 5 asked whether there were differences in demographic characteristics between those who did and didn't provide blood samples. I think it is also important to comment on whether there were differences in characteristics between those who were lost to follow-up and those who attended 3, 12 and 24 month visits. This would help with understanding the generalisability of findings.*

In response to this reviewer, we have examined interactions between intervention group and individual baseline characteristics (age, BMI, Sex, household income, ethnicity and education) for attendance at each study visit (3 months, 12 months and 24 months). Only two interactions were statistically significant (gender and intervention at 12 months ($p=0.008$), education and intervention group at 24 months ($p=0.046$)). However, neither interaction demonstrated a consistent pattern across visits. We have added a sentence to the paper to state that "Examination of the effect of individual characteristics on attendance by intervention group found no statistical evidence of bias in attendance over the study's duration." P10 L16

7. *The authors need to make it clear in the methods that the comparisons between the BI and combined CP groups are one-sided tests, and the comparisons between the two CP groups are two-sided tests. It is mentioned in the table (and in the protocol) but I think it should be stated in the statistical analysis methods as well.*

We have added this specification to the analysis section P8 L3-4

8. *I am not a modeller or health economist but the results from the 25 year modelling seem surprising to me. Since the general trend in all groups is for participants to regain the weight they have lost, can the longer time period for which the individuals in the 52 week intervention group are at a weight below their baseline (on average) really lead to such big improvements in terms of incident cases of disease, QALYs etc over a 25 year period? Will defer to an economist to assess this but I would be interested to know whether the authors were surprised by this?*

We were not overly surprised by the results of the modelling. Weight losses are similar to the Diabetes Prevention Programme, which saw a 27% reduction over 15 years, despite gradual weight regain. Naturally these are estimates based on a number of assumptions. However, our assumptions are relatively conservative (e.g. assuming 100% weight regain by 5 years).

9. *It seems surprising that "Only a tiny minority of participants in each arm used interventions that were not indicated by their randomisation." I found this slightly confusing as it implies that hardly anyone in the 12 week programme chose to carry on with it to say 52 weeks under their own steam (which to me would be contra-indicated by their randomisation)? But this isn't the case because later in the discussion figures on how many continued under their own cost are presented. Perhaps it should be made clear that this sentence is talking about use of other interventions during the period that participants were receiving the programme they were allocated to (if that is what is meant?)*

We have amended to be more specific about what we mean. "Only a tiny minority of participants in each arm used other NHS interventions or weight loss medications, and only a small proportion of participants who were assigned to the brief intervention group went on to use a commercial weight loss programme."

10. *CONSORT checklist is not included.*

The CONSORT checklist is attached.

Minor points

1. *In the abstract it states that "Behavioural programme participants lost more weight than brief intervention participants [adjusted difference = -2.71 kg (95% CI -3.86,-1.55); p<0.0001]." It would be helpful to explain what was adjusted for so that the abstract may stand alone.*

This has been added to the abstract P3 L13

2. *Out of interest, how many in the 52-week group were still attending at 24 months?*
17% - This is reported in Table 5

3. *Table 2 title "Table 2: Changes in weight from baseline (mean, SE) at 3, 12, and 24 months by intervention group using different assumptions about missing data" only seems to show results under the assumption of MAR...*

The title has been amended to be clear it only reports the main analysis

4. *Table 3. Would be useful to label which data in the table relate to the 5% and 10% loss.*

Apologies for this omission. This column has now been added to the table.

Reviewer #8: As recognized by the authors, previous reviewers and editors, the addition of economic evaluation to this manuscript provides added insight into the relative value of these interventions. I commend the authors for presenting both a person-level cost-effectiveness analysis using data from the trial as well as completing a model-based cost-utility analysis over a 25 year time horizon. Based on the editors request I have restricted my commentary to the additional economic evaluations that have been supplemented to this manuscript - expanded manuscript body and new supplemental appendix.

Major Comments

* *While it is clear in the manuscript body, I would suggest the authors more clearly state in the abstract that 2 economic evaluations were performed, one with a 2 year time-horizon using person-level data from the trial and a second with a 25-year time horizon using microsimulation modelling.*

We have amended the abstract as suggested. P3 L16.

* *The authors offer insufficient detail regarding the model structure. What health states were modeled over the 25 year time horizon? As per ISPOR economic evaluation reporting guidelines (<https://www.ispor.org/ValueInHealth/ShowValueInHealth.aspx?issue=3D35FDBC-D569-431D-8C27-378B8F99EC67>), a figure to show model structure is strongly recommended.*

**With respect to model inputs for the 25-year analysis, the authors must provide some description of QALY calculations beyond simply referencing the use of the Foresight: Tackling Obesities framework. From where were the utility weights drawn? Can the authors expand on how the population's disease incidence was projected? The manuscript body and appendix offer little insight into the model inputs.*

A figure illustrating model structure and an associated description have been added to section 4.1 of the Web Appendix to clarify the model structure and microsimulation process, specifically paragraphs 2 and 3. We have also added a table of the model inputs.

* *Characterization of uncertainty in the microsimulation model should be presented (e.g. cost-effectiveness plane and cost-effectiveness acceptability curve)*

The confidence limits that accompany the sets of output data in the web appendix represent the accuracy of the microsimulation (monte carlo errors) as opposed to the confidence of the input data (sensitivity analysis) itself. Errors around all of the input data were not available. Because this does not offer a complete picture of uncertainty, it would be preferable to only report the point estimates obtained, so as to avoid the uncertainty estimates being misinterpreted.

We have amended the Web Appendix (section 4.1 Methods): "The microsimulation model does not currently produce estimates of uncertainty based on input data statistics (sensitivity analysis). However, the model does produce uncertainty arising from the Monte Carlo process, representing the accuracy of the microsimulation itself."

Specific comments

* *"Cost per kg" or "cost/kg" is used throughout the manuscript and appendix when in fact, "incremental cost per kg lost" would be more appropriate. Those not familiar with economic evaluation may mistakenly interpret the "cost per kg" to reflect the cost associated with losing 1 kg associated with one weight loss intervention. In fact the authors are appropriately using the ICER (incremental cost effectiveness ratio or incremental cost per kg lost in this case) as the primary outcome parameter. As an example, Figure A1 titled "Cost effectiveness plane - Cost per additional kg lost (2-year time horizon)" should be more clearly titled as "Cost effectiveness plane - Incremental cost per additional kg lost (2-year time horizon)"*

We thank the reviewer for highlighting this issue and have amended for clarity

**In Appendix, point 4 - Long Term Cost-Effectiveness Modeling, 2nd paragraph: "For a given comparison of A vs B, negative ICERs indicate that the intervention is dominant in terms of cost-effectiveness, over group B" This is not entirely true. A negative ICER may also reflect that A is more expensive and less effective than B, whereby B is dominant.*

This additional information has been added to the Web Appendix, section 4.1, for clarity.

ADDITIONAL EDITS

While completing the COI forms, Prof Jebb realised that her COI regarding the Rosemary Conley articles "timed out" this month, and so the sentence "Until January 2014, SAJ wrote a nutrition column for the Rosemary Conley Diet and Fitness magazine and received a fee." has been removed from the COI section of the manuscript. P2

We previously omitted a statement about adverse events from the body of the manuscript (it was in the abstract) so have added this on P7 and P12.

We previously omitted the long term cost-effectiveness result for the 12-week programme from the discussion and the research in context panel, so we have added sentences on P13 and P21.

We have highlighted our use of a flat rate cost in the cost-effectiveness analysis, as this is not always how this programme is charged and may overestimate real costs. P13.

We have highlighted an additional limitation on P14 (the low completion of health care usage data)

We have added updated references for the Diabetes Prevention Programme Study (reporting the 15 year, rather than 10 year findings) on P15 and the UK Census Data P14.

We have updated the literature review for the Research in Context Panel and changed the date in the manuscript to today's date (P21).

We have moved the sentence "Contrary to common criticisms that these interventions could exacerbate health inequalities, there was no evidence that the outcome of treatment is moderated by socioeconomic factors such as gender, education and income." to be next to the weight loss outcomes, as this is the treatment outcome that we refer to. (P21)

Extended and standard duration weight loss referrals for adults in primary care (WRAP): a pragmatic randomised controlled trial.

Authors

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Contribution

ALA is the Chief Investigator. ALA, SAJ, PA, JCGH, MS, and SRC are grant holders. ALA and SAJ developed the research questions and designed the trial and PA, JCGH, MS, SRC, AM and AMT contributed to the design of the protocol. ALA, PA, JCGH, EJB, AMT, MT, JW, BRM, SAJ were responsible for data collection. JW and AT were the Trial Managers. DC was responsible for data management. GMW conducted the statistical analyses with input from AM. LI analysed the within-trial cost-effectiveness and attendance data with input from MS and DT. LP, LR, AJ, and LW conducted the microsimulation analyses. ALA, GMW, AM, PA, EJB, JCGH, SAJ, MS, LI, DT, LP, LR, LW, AJ contributed to the interpretation of data. ALA wrote the first draft of the manuscript. All authors contributed to the writing and critical revision of the manuscript.

Conflicts of Interest

ALA, SAJ, EJB, BRM and JCGH have received research funding to their institutions from Weight Watchers International and have given and received hospitality from providers of

1 commercial weight loss services on a small number of occasions. PA and SAJ have
2 conducted another publicly funded trial in which part of the intervention was delivered by
3 and donated free by Slimming World and Rosemary Conley, and they are principal
4 investigators on a trial funded through a grant to the University of Oxford from
5 Cambridge Weight Plan. ~~Until January 2014, SAJ wrote a nutrition column for the~~
6 ~~Rosemary Conley Diet and Fitness magazine and received a fee.~~ JCGH is Principal
7 Investigator on studies funded through research grants to the University of Liverpool
8 from the California Prune Board, Ingredion and American Beverage Association (ABA),
9 and has studentships funded through BBSRC and ESRC with Unilever, Coca-Cola, and
10 Tate & Lyle. JCGH provides expertise on health, weight management and appetite
11 control to the food and beverage, commercial weight management, pharmaceutical and
12 ingredient sectors.

13

14

Summary

Background

There is good evidence that primary care referral to an open-group behavioural programme is an effective treatment for obesity, but little evidence on optimal treatment duration.

Methods

In this non-blinded parallel-group randomised controlled trial, we recruited participants (age ≥ 18 years, BMI ≥ 28 kg/m²) through 23 primary care practices in England. Participants were randomised using the study database in a 2:5:5 allocation to: brief weight loss intervention, a weight management programme (Weight Watchers®) for 12 weeks, or the same weight management programme for 52-weeks. We followed participants over two years. The primary outcome was weight at one year, analysed using mixed-effects models according to intention-to-treat principles **adjusted for centre and baseline weight**. In a hierarchical-closed-testing procedure we compared combined behavioural programme arms with brief intervention, then compared the 12-week and 52-week programmes. **We conducted a within-trial cost-effectiveness analysis using person-level data and modelled outcomes over a 25-year horizon using microsimulation**. Current Controlled Trials ISRCTN82857232.

Findings

Between 18th October 2012 and 10th February 2014, 1267 eligible participants were randomised to the brief intervention (211), 12-week programme (528) and 52-week programme (528). 823 (65%) completed an assessment at one year and 856 (68%) at two years. All participants were included in the analyses. At one year, mean weight change was -3.26 kg (brief intervention), -4.75 kg (12-week programme), and -6.76 kg (52-week programme). Participants in the behavioural programme lost more weight than those in the brief intervention [adjusted difference = -2.71 kg (95% CI -3.86, -1.55); $p < 0.0001$]. The 52-week programme was more effective than the 12-week programme [adjusted difference = -2.14 kg (95% CI -3.05, -1.22); $p < 0.0001$]. Differences between groups were still significant at two years. No adverse events related to the intervention were reported. Over two years, the incremental cost-effectiveness ratio (ICER; compared with brief intervention) was £159/kg lost for the 52-week programme and £91/kg for the 12-week programme. Modelled over 25 years after baseline, the ICER for the 12-week programme was dominant compared with the brief intervention. The ICER for the 52-week programme was cost-effective compared with the brief intervention (£2498/QALY) and the 12-week programme (£3804/QALY).

Interpretation

For adults with overweight or obesity, referral to this open-group behavioural weight loss programme for at least 12 weeks is more effective than brief advice and self-help materials. A 52-week programme produces greater weight loss and other clinical benefits than a 12-week programme and, although it costs more, modelling suggests it is cost-effective in the longer term.

Funding

- 1 This trial was funded by the National Prevention Research Initiative grant MR/J000493/1.
- 2 The cost of the Weight Watchers® programme and the costs of blood sampling and
- 3 analysis were funded by Weight Watchers International as part of an MRC Industrial
- 4 Collaboration Award.

BACKGROUND

The burden of disease attributable to excess weight places considerable strain on health care resources across the world.^{1,2} Behavioural weight management programmes are the first-line treatment for overweight and obesity, and although there is good evidence that some of these programmes can be effective, others are not.³ This may be due to differences in content and format of interventions, including the length of time support is provided. In the UK, the National Institute for Health and Care Excellence (NICE) public health guidance recommends that behavioural weight management programmes should last a minimum of 12 weeks⁴ and this is the standard length of the most commonly commissioned interventions.⁵ However, there is conflicting evidence about whether longer treatment duration would be more effective.^{6,7}

Open-group behavioural weight loss programmes are among the most commonly commissioned programmes in the UK and evidence suggests these programmes are effective and cost-effective.^{3,8} The current trial was designed to directly compare whether 52-week referral to an open-group weight management programme would achieve significantly greater weight loss and improvements in a range of secondary health outcomes than the current practice of 12-week referrals, and be more cost-effective.

METHODS

Study Design

This was a multi-centre, non-blinded, multi-arm parallel groups randomised controlled trial with imbalanced randomisation (2:5:5), conducted in England. The full protocol is described elsewhere.⁹

In brief, participants were recruited from 23 primary care practices across England between October 2012 and February 2014. Recruitment and follow up was conducted by three research centres: MRC Human Nutrition Research, Cambridge (coordinating centre), the University of Liverpool, and the University of Oxford. Cambridge and Liverpool teams recruited local practices and research staff conducted study visits at the research centre. Oxford recruited practices across southern and eastern England and practice staff (usually a research nurse) conducted study visits at the practice.

Ethical approval was received from NRES Committee East of England (12/EE/0363). This trial was registered at Current Controlled Trials ISRCTN85485463 on 12th October 2012.

Participants

Eligible participants (aged ≥ 18 years; body mass index (BMI) ≥ 28 kg/m²) were identified through practice records. Exclusion criteria were: planned (within two years) or current pregnancy; previous or planned bariatric surgery; currently following a structured, monitored weight-loss programme; participating in other research that could confound outcome measures; eating disorder; non-English speaking or with special communication needs. Practices could exclude additional patients they felt it was inappropriate to invite but were asked to report reasons. These additional exclusions included terminal illness/palliative care, dementia, a severe mental health problem or learning difficulty, carer for a terminally ill relative, or recently bereaved. Patients were invited by letter and asked to contact the local study coordinator for telephone screening if they were interested in participating. Eligible and willing participants were given an appointment, where a member of the research team weighed them and measured their height to confirm eligibility before randomisation. Where more than one household member was eligible and interested in participating, the first to enrol was taken as the participant. All participants gave written informed consent.

Randomisation and Masking

Participant details were entered into the trial database, which automatically assigned participants with a valid measured BMI to one of the three interventions (brief intervention, referral to the commercial open-group behavioural weight loss programme (behavioural programme) for 12 weeks, or referral to the same programme for 52 weeks) in a 2:5:5 allocation stratified by centre and gender, with a block size of 12. The randomisation sequence was generated by the trial statistician using Stata 12.1 and programmed into the database by the Data Manager. The sequence was unknown to research staff and participants. Once participants were enrolled and entered into the database, the database revealed the group allocation. Due to the nature of the intervention and the trial design, participants and research staff were not blinded to the intervention allocation after randomisation.

Procedures

Participants randomised to the behavioural programme were asked to attend a local Weight Watchers (WW) meeting once a week for the duration of their intervention (12 weeks or 52 weeks). At their baseline visit they were given a list of local meeting times and locations, a voucher booklet for 12 visits (the expiry date was set for 14 weeks from baseline) and a unique code to access digital tools for the duration of their intervention. Meeting vouchers were identical to those used in the National Health Service (NHS) referral schemes operating elsewhere in the country and allowed participants to attend meetings without charge. At the meeting, they gave the voucher to the group leader, but

1 were asked not to mention their participation in the trial to the group leader or other
2 members. Participants in the 52-week programme group were given a further three
3 books of vouchers when they returned for their 3 month visit (expiry date set for 54
4 weeks from baseline).

5 Participants allocated to the brief intervention were given a 32-page printed British Heart
6 Foundation booklet of self-help weight management strategies¹⁰ and research staff read
7 a scripted introduction that drew attention to each section of the booklet.

8 All participants attended measurement appointments at 0, 3, 12, and 24 months. Height
9 was measured to the nearest 0.1 cm using a stadiometer. Weight and fat mass were
10 measured to the nearest 0.1 kg using a 4-point Tanita segmental body composition
11 analyser. Waist circumference was measured to the nearest 0.1 cm using a tape
12 measure, half way between the lowest rib and the iliac crest. Blood pressure was
13 measured three times in a seated resting state using an automated blood pressure
14 monitor, and the mean calculated. Biochemical measurements were optional. Willing
15 participants were asked to give a fasting blood sample at 0 and 12 months for analysis
16 of glucose, glycosylated haemoglobin (HbA_{1c}) and lipid profile. All samples were analysed
17 in Cambridge using standardised methods (web appendix).

18 At each visit, participants self-reported their use of weight loss methods, including the
19 allocated intervention, and completed the EQ5D-3L^{11,12} as a measure of quality of life.
20 Data on health care resource use was also self-reported. Participants who were unable or
21 unwilling to attend a 12 month visit (primary outcome measurement) were asked to
22 provide a self-measured weight by phone or email. Self-reported weights are not
23 included in the primary outcome analysis but are included in a sensitivity analysis (web
24 appendix).

25 **Outcomes**

26 The primary outcome was change in body weight at 12 months. The secondary clinical
27 outcomes were: body weight at 3 and 24 months; proportion of participants losing $\geq 5\%$
28 body weight or $\geq 10\%$ of baseline body weight at 3, 12 and 24 months; waist
29 circumference, fat mass, and blood pressure at 3, 12 and 24 months; fasting blood
30 glucose, HbA_{1c}, triglycerides and HDL, LDL, and total cholesterol at 12 months; and self-
31 reported quality of life (EQ5D-3L) and health resource use at 3, 12 and 24 months. We
32 did not anticipate that adverse events related to the interventions would occur and so
33 did not formally record these.

34 **Statistical Analysis**

1 The sample size was calculated based on data from our previous trials^{13,14} with an
2 expected difference of 2.3 kg between the brief intervention and combined behavioural
3 programme groups, 1.3 kg difference between 12-week and 52-week programmes, and
4 an assumed standard deviation of 6 kg. The hierarchical-closed-testing procedure
5 compared the behavioural programme arms with brief intervention using a one-sided
6 test and then, only if significant at the 5% level, conducted a two-sided test for a
7 difference between 12-week and 52-week programmes in order to preserve a type I
8 error rate of 5% without the need for a multiplicity correction. With a sample of 1200
9 participants allocated as 200 (brief intervention), 500 (12-week programme), and 500
10 (52-week programme), we had 99.95% power to detect a difference of 2.3 kg between
11 brief intervention and the behavioural programmes, and 92.87% power to detect a
12 difference of 1.3 kg between 12-week and 52-week programmes. The overall power of
13 the study was 92.82%.

14 Analyses were pre-specified in the published protocol.⁹ The primary analyses evaluated
15 differences between the intervention groups in mean weight change from baseline to
16 12 months. Given levels of attrition commonly encountered in weight-loss trials, four
17 analysis approaches were taken to account for the impact of missing data: a missing at
18 random (MAR) analysis using a variance components model; a completers only analysis;
19 baseline observation carried forward (BOCF); and last observation carried forward
20 (LOCF). For the MAR analysis, mean weight losses and their standard errors were
21 obtained via a multiple imputation model using multivariate normal regression; 20 data
22 sets for weight were imputed separately for each treatment group, with baseline weight,
23 3-month weight, 12-month weight, and 24-month weight regressed on centre. A model
24 for multivariate normal data with baseline weight, 3-month weight, 12-month weight,
25 24-month weight as the outcome was fitted using measured weights at each time point
26 via generalised least squares, with intervention group, visit, intervention group-by-visit
27 interaction and centre included as fixed effects. For the completers only, BOCF and
28 LOCF analyses, fixed effect models for continuous normal data were fitted to the 12-
29 month weight data. The fixed effects were intervention group, centre and baseline
30 weight. Analyses of secondary outcomes were conducted using the same regression
31 based models. Data reported in the body of the paper used the MAR assumption. The
32 web appendix contains analyses by all four methods. Sensitivity analyses were
33 conducted to examine whether findings were sensitive to timing of the 12-month
34 assessment or the inclusion of self-reported weights. All analyses were conducted using
35 Stata 13.1.

36 A recent review highlighted the lack of evidence of this type of programme on socio-
37 economic inequalities⁴, so we also conducted a post-hoc analysis of potential interactions

between intervention effects and gender, educational qualification and income. Coefficient estimates and their 95% confidence intervals were calculated for each fixed effect.

To establish within-trial cost-effectiveness over 24 months, we calculated the incremental cost-effectiveness ratio (ICER) as incremental cost per additional kg weight loss (see web appendix for full details). If the participant attended at least one session, the NHS would be charged a flat rate of £48.50 (12-week programme) or £190 (52-week programme). If they did not attend, there was no charge. Non-intervention NHS costs were estimated from health resource use questionnaires, which were completed by participants at baseline, 3, 12, and 24 months and were framed within a three months recall period.¹⁵ To ascertain the full NHS costs incurred over the 24 months follow-up period we applied area under the curve methods.¹⁶ A secondary analysis examined the ICER over a 1-year time horizon, to enable comparability with similar studies with shorter follow up.

We used the microsimulation model developed for the Foresight: Tackling Obesities project^{17,18} to estimate the effect of the three interventions on disease incidence, healthcare costs, quality adjusted life-years (QALY), and ICERs for 25 years following baseline (web appendix). This analysis used mean change in BMI for each intervention at 1 and 2 years, and assumed that between 2 and 5 years all participants returned to their baseline weight in a linear manner (i.e. regained all weight lost) and then followed national trends based on data derived from repeated cross-sectional samples in the Health Survey for England.¹⁹

The number of meetings attended by the participants in the behavioural programme groups between baseline and 3 months, 9 months and 12 months, and 21 months and 24 months, was self-reported. The proportion of participants who self-reported utilising other weight loss interventions was also calculated.

Data management was overseen by the coordinating centre's data manager. The data set linking treatment group to participant outcomes was only released to the investigators following completion of data collection for the primary outcome.

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The funders of the study had no role in the design, data collection, data analysis, data interpretation, or writing of the report. ALA and GMW had full access to all data and ALA had final responsibility for the decision to submit for publication.

RESULTS

Between 18th October 2012 and 10th February 2014, 1954 participants were screened and 1269 were eligible and agreed to randomisation (Figure 1). Shortly after the baseline appointment, two enrolled participants were excluded because their GP reported illnesses that would have excluded them. These participants were removed and the remaining 1267 participants were included in the primary analyses. Data on participants who died during the trial is included up until the event. The number of participants completing each assessment was 1004 (79%) at 3 months, 823 (65%) at 12-months assessment, and 856 (68%) at 24-months. Using Pearson's chi-squared test, there was a borderline statistically significant association between the percentage of participants attending the 12-month appointment and intervention group ($p=0.0475$), though there was little evidence to suggest such an association for participants completing the 24-month assessment ($p=0.21$). Examination of the effect of individual characteristics on attendance by intervention group found no statistical evidence of bias in attendance over the study's duration. Analyses of biochemical risk factors are based on 837 participants (66%) who provided a blood sample at baseline.

Table 1 shows baseline characteristics by intervention group. Participants had a mean BMI of 34.5 kg/m^2 (SD 5.2), a mean age of 53.2 years (SD 13.8), 68% were female, 90% were White, 15% had diabetes, 50% had hypertension.

Figure 2 shows the weight trajectories of the three intervention groups at each time point using all measured weights. Mean (SE) weight change at 3 months was -2.04 kg (0.30) following brief intervention, -4.84 kg (0.21) in the 12-week programme, and -4.62 kg (0.18) in the 52-week programme. Participants in the combined behavioural programme arms lost more weight than those in the brief intervention [adjusted difference = -2.67 kg (95% CI $-3.28, -2.07$); $p < 0.0001$] and there was no significant difference between the 12-week and 52-week programmes [adjusted difference = 0.22 kg (95% CI $-0.26, 0.69$); $p = 0.371$]. Mean weight change at 12 months, the primary outcome, was -3.26 kg (0.68) in brief intervention, -4.75 kg (0.35) in the 12-week programme, and -6.76 kg (0.42) in the 52-week programme (Table 2). Participants in the combined behavioural programme arms lost significantly more weight at 12 months than those receiving a brief intervention [adjusted difference = -2.71 kg (95% CI $-3.86, -1.55$); $p < 0.0001$] and participants in the 52-week programme lost significantly more weight than those in the 12-week programme [adjusted difference = -2.14 kg (95% CI $-3.05, -1.22$); $p < 0.0001$]. On average, participants in all groups regained weight between 12 and 24 months but the differences between groups remained significant. Weight change between baseline and 24 months was -2.30 kg (0.73) in brief intervention, -3.00

kg (0.37) in the 12-week programme, and -4.29 kg (0.44) in the 52-week programme. Participants randomised to the behavioural programme lost significantly more weight than those receiving a brief intervention [adjusted difference = -1.44 kg (95% CI -2.87, -0.00); $p=0.0247$]. Participants randomised to the 52-week programme lost significantly more weight than those receiving the 12-week programme [adjusted difference = -1.32 kg (95% CI -2.46, -0.18); $p=0.0231$].

Participants randomised to the 12-week programme lost significantly more weight than the brief intervention group at 3 months [adjusted difference=-2.79kg (-3.44,-2.13); $p<0.0001$] and 12 months [adjusted difference=-1.61kg (-2.84, -0.38); $p=0.0105$] but there was no significant difference in weight loss between these groups at 24 months [adjusted difference = -0.74 kg (95% CI -2.45, 0.77); $p=0.338$].

Sensitivity analyses examining weight change with alternative assumptions about missing data gave similar results (web appendix). Research centre was not a significant predictor of weight change in any of the models. There was no evidence suggestion that the intervention effect differed by participant gender ($p=0.48$), educational attainment ($p=0.79$), or household income ($p=0.64$).

The percentage of participants losing $\geq 5\%$ and $\geq 10\%$ weight, and the relative risk between groups is shown in Table 3. At 12-month follow up, 57% of participants in the 52-week programme had lost $\geq 5\%$ of weight, compared with 42% in the 12-week programme and 25% in the brief intervention. Participants in the behavioural programme were significantly more likely than the brief intervention group to lose $\geq 5\%$ and $\geq 10\%$ body weight. Participants in the 52-week programme were significantly more likely than those in the 12-week programme to lose $\geq 5\%$ and $\geq 10\%$ weight.

At 12 and 24 months, participants in the 52-week programme had greater reductions in waist and fat mass than participants in the 12-week programme or brief intervention group (Table 4). At 12 months, participants in the 52-week programme had greater reductions in HbA_{1c} than those in the 12-week programme [adjusted difference=-1.31 mmol/mol (95% CI -2.47, -0.15); $p=0.0268$] and brief intervention [adjusted difference=-2.65 mmol/mol (95% CI -4.28, -1.01); $p=0.0015$] and greater reductions in fasting plasma glucose than those in the 12-week programme [adjusted difference=-0.29 mmol/L (95% CI -0.58, -0.00); $p=0.0497$] and brief intervention [adjusted difference=-0.46 mmol/L (95% CI -0.88,-0.03); $p=0.0342$]. There were no significant differences between the 12-week programme and brief intervention for either HbA_{1c} or fasting glucose. Changes over time in blood pressure, quality of life, triglycerides and

HDL, LDL and total cholesterol were small and there were no significant differences between groups. No participants reported adverse events related to the intervention.

Intervention usage is summarised in Table 5. At 3 months, 5% participants in the brief intervention group had attended a commercial weight management programme, compared with 68% in the 12-week programme and 69% in the 52-week programme. Only 1% of participants in all groups attended an NHS-led programme and less than 1% used weight-loss medication. For participants referred to the behavioural programmes, the mean number of sessions attended was 8.4 (SD 4.2) in the 12-week programme and 28.2 (SD 14.8) in the 52-week programme. Full details of the economic evaluation are in the web appendix. In brief, intervention costs, including GP referral time, are estimated as £18.50 (brief intervention), £60 (12-week programme) and £195 (52-week programme). There were no significant differences between groups in health care resource use per participant at baseline and throughout follow-up. The estimated incremental NHS cost per additional kg weight loss (expressed here as £/kg) was £91/kg for the 12-week programme and £159/kg for the 52-week programme. Analysis using a 1-year time horizon for consistency with other studies, reduced the ICER to £26/kg and £75/kg respectively.

The cost-effectiveness acceptability curve (CEAC, web appendix Figure A2) is based on weight loss at 2 years and includes all NHS costs incurred during that time. If decision-makers are willing to pay at least £60/kg, then the 12-week programme would be the preferred strategy. If decision-makers are willing to pay £200/kg, then the 52-week is the preferred strategy. If costs are restricted to intervention-only costs, the 52-week programme becomes the preferred strategy at £100/kg.

Microsimulation modelling estimated that over 25 years after the baseline year, the 12-week programme was cost-saving (dominant) compared with the brief intervention. The 52-week programme was cost-effective relative to both the brief intervention (ICER = £2498/QALY) and the 12-week programme (£3804/QALY).

In comparison to the brief intervention, the 12-week programme resulted in 623 fewer incident cases of disease, 643 additional QALYs, and a cost-saving of approximately £68,000 per 100,000 individuals. In comparison to the 12-week programme, the 52-week programme resulted in 1786 fewer incident cases of disease and generated 1282 additional QALYS, at a cost of approximately £4.9 million per 100,000 individuals. Further details are included in the web appendix.

DISCUSSION

Adults in primary care with overweight or obesity who were referred to an open-group behavioural weight management programme lost 2.7 kg (± 1.2) more weight at 1-year follow up than those who were given brief advice and self-help materials. Those who were referred to this behavioural programme for 52-weeks lost 2.1 kg (± 0.9) more weight than those who were referred for 12 weeks. Fifty-seven percent of participants referred to the 52-week programme lost more than 5% weight, compared with 42% referred to the 12-week programme and 25% of those in the brief intervention group. Five percent is often used as a cut-off for clinically significant weight loss, although even smaller weight losses are associated with improvements in markers of cardiovascular disease risk.²⁰ On average all groups regained some of the weight lost and at 2-years the difference in weight loss between the 12-week programme and the brief intervention was no longer significant, whereas the weight loss in the 52-week programme was significantly greater than both other groups. Participants in the 52-week programme also had larger reductions in waist circumference, fat mass, fasting glucose and HbA_{1c} than participants in the 12-week programme and the brief intervention. When the impact of the 12-week programme was modelled over 25 years, it was cost-saving compared with the brief intervention. Although the 52-week programme was more expensive in the within-trial analysis, when the impact was modelled over 25 years, it resulted in the greatest gain in QALYs and the greatest reduction in disease incidence. By standards set by the National Institute of Health and Care Excellence, the intervention is cost-effective in comparison to both the brief intervention and the 12-week programme. It should be noted that this assessment of cost-effectiveness does not include potential further savings in social care and indirect healthcare costs. It also uses a flat rate cost for each intervention, when in practice full costs would not be incurred if people did not complete the course, thus potentially overestimating intervention costs.

A strength of this trial is the large patient group that is broadly generalisable to the UK population. In our previous trial¹³, participants with a BMI 27-35 kg/m² were identified during routine consultations and recruited to the trial. The current trial was more inclusive (BMI 28-68 kg/m²) and participants were recruited by letter based on weight records. In the former, the mean BMI was 31.4 kg/m² whereas in the present study participants had a mean BMI of 34.5 kg/m², more comparable to the population typically referred to open-group behavioural programmes in NHS referral schemes.²¹ Mailing invitations to all eligible patients resulted in a higher proportion of male participants than seen in routine referral schemes,^{13,21} although this is still lower than the proportion of males in the UK population.²² More than half of participating practices were from areas with an index of multiple deprivation that is higher (more deprived) than the national

1 median and participants were drawn from a wide range of socioeconomic groups.²³ Most
2 participants were white, with the proportion enrolled reflecting the ethnic make-up of the
3 UK.²² There was no evidence that the intervention effects varied by gender or socio-
4 economic status. This is striking given oft-repeated views that these interventions are
5 not appropriate for men and concerns that individual behavioural interventions
6 exacerbate socio-economic inequalities in health.^{24 25} Taken together, the findings
7 suggest that the intervention effects reported here may be generalisable to the UK adult
8 population. Although uptake of the programmes by more deprived populations is
9 somewhat lower than in less deprived areas²³, more targeted schemes, as have been
10 implemented elsewhere¹⁴, might reduce health inequalities.

11
12 Loss to follow up at 1 year was slightly below average for weight loss trials,²⁶ and there
13 was little attrition between 1 and 2 years. Three different intention-to-treat analyses
14 were conducted that each make different assumptions about missing data, as well as two
15 sensitivity analyses. The consistency of effects demonstrates the robustness of our
16 findings. The pragmatic nature of the trial meant that participants in all groups were free
17 to use other weight-loss methods during the trial. This reflects how these interventions
18 are routinely delivered and allows direct translation of these findings to clinical practice.
19 Only a tiny minority of participants in each arm used other NHS interventions or weight-
20 loss medications, and only a small proportion of participants who were assigned to the
21 brief intervention group went on to use a commercial weight loss programme. A strength
22 of this trial is the 2-year follow up of participants, which gives important information on
23 weight trajectories after treatment ends. The modelled cost-effectiveness over 25 years
24 is based on assumptions about weight trajectories beyond 2 years, however we have
25 been relatively conservative in these assumptions, assuming all weight lost is regained
26 within 5 years. The within-trial ICERs are strongly affected by non-significant differences
27 between groups in healthcare costs (highest in the 52-week programme and lowest in
28 the 12-week programme) based on health-care usage data in 46.7% participants.
29 However, sensitivity analyses (web appendix) provide information with which to assess
30 the strength of these findings. Fasting status when blood was taken and attendance at
31 Weight Watchers were self-reported and could be susceptible to reporting/recall bias.
32 Reliance on subjects confirming that the blood sample was taken in a fasting state is a
33 universal concern in any free-living study and findings related to glucose were congruent
34 with findings for HbA_{1c}, which is not affected by fasting status. Attendance at Weight
35 Watchers was self-reported and could be susceptible to reporting/recall bias. However,
36 any bias in the attendance data does not impact the pre-specified outcomes which were
37 conducted on an intention-to treat basis.

1 The weight losses seen in this study are consistent with previous trials of 12 weeks and
2 52 weeks referral to commercial open-group behavioural weight management
3 programmes, suggesting findings are robust.^{13,14,27} Estimates of the mean **incremental**
4 cost per **additional** kg lost for either duration of treatment are within the range of other
5 behavioural programmes (web appendix Table A4). The reductions in fasting glucose and
6 HbA_{1c} were not seen in our previous trial of the 52-week programme,²⁸ perhaps because
7 the lower baseline BMI and stricter inclusion criteria in that study meant that participants
8 had lower baseline values. Almost half of participants in the current trial had elevated
9 fasting glucose and/or HbA_{1c} at baseline. Reductions seen in the 52-week programme
10 participants at 12 months (-0.5 mmol/l fasting glucose and -2.8 mmol/mol HbA_{1c}) are
11 larger than those seen at the same timepoint in the intensive lifestyle intervention arm
12 of the Diabetes Prevention Programme (DPP; approximately -0.4 mmol/l fasting glucose
13 and -1 mmol/mol HbA_{1c})²⁹, whose participants were similar to those in the current study
14 in baseline BMI, HbA_{1c} and glucose and had similar weight loss at 12 months, but
15 achieved at a fraction of the cost.³⁰ **Notwithstanding gradual weight regain and increase**
16 **in associated risk factors observed over 15 years follow-up, DPP achieved a 27%**
17 **reduction in the cumulative incidence of diabetes in the lifestyle intervention relative to**
18 **the control group.**³¹ However the impact of these more scalable interventions on
19 diabetes incidence will depend on whether longer term weight trajectories are similar.

20 The programme we evaluated is widely available and participants in the brief
21 intervention group were neither encouraged nor discouraged from attending other
22 weight loss programmes. Only 1 in 20 chose to do so, compared with 14 in 20 of those
23 referred to these programmes. In the 12 week group, 19% of participants were still
24 attending the programme 12 months later at their own cost, compared with 9% of those
25 in the brief intervention. This suggests some legacy effect of the initial referral. However,
26 this is lower than the 42% of participants in the 52-week group who were still attending
27 at 12 months. As the median household income was about £30,000, it is likely that
28 many people would have been able to pay the cost of the programme (approximately
29 £5/week) suggesting it may be the act of referral itself that is the source of motivation
30 to attend, though it is impossible to exclude that lower attendance in other groups was
31 related to the cost. The importance of the referral is supported by qualitative data that
32 found the GP referral is perceived as an implicit recommendation of the programme and
33 the allocation of NHS resources to enabling their attendance increases motivation to
34 attend.³² It is also supported by another trial among people with obesity attending a GP
35 consultation unrelated to their weight, where 77% who agreed to participate in the trial
36 and were offered a referral to a weight management programme accepted it and 40%
37 attended.³³

1 The absolute weight loss among participants receiving only the brief intervention
2 warrants consideration. Participants given 5 minutes of non-tailored advice and a self-
3 help booklet lost over 3 kg at 12 months and over 2 kg at 24 months. Weight change in
4 this group is larger than the average weight loss observed in a recent meta-analysis³ for
5 interventions led by generalist primary care teams, and larger than the average weight
6 loss seen in a systematic review of self-help interventions.³⁴ Given the small cost of this
7 intervention (self-help booklet and three short appointments that could be delivered by a
8 nurse or health care assistant), observational data would support the implementation of
9 this intervention as a minimal standard in primary care. However, this finding highlights
10 the importance of including a control group when evaluating weight loss interventions. A
11 recent review has shown that control groups given minimal interventions will generally
12 lose weight over the course of a trial.³⁵ In this review there was considerable
13 heterogeneity in the absolute weight loss of control groups, which may reflect differences
14 in study populations and trial design. The current trial illustrates this showing 3.4 kg
15 weight loss in a minimal contact control group, when an almost identical brief
16 intervention achieved less than 1 kg weight loss when used as a control group in a
17 different population and context.³⁶

18 This trial demonstrates that referral to this commercial open-group behavioural weight
19 loss programme increases weight loss relative to a brief intervention in primary care.
20 Increasing the duration of the programme from 12 weeks to 52 weeks increases weight
21 loss and improvements in other markers of diabetes and cardiovascular risk, most
22 notably glycosylated haemoglobin and fasting glucose. Economic evaluation of this trial
23 found that while the 52-week programme requires greater initial investment, it is cost-
24 effective in the longer-term and commissioners should consider a move towards
25 extended referral schemes.

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Research in context panel

Evidence before this study

A systematic review and meta-analysis conducted in November 2012 synthesised data from 37 trials of behavioural weight management programmes delivered in a context that could be replicated in routine clinical practice. Three studies evaluated primary care referral to a commercial open-group programme in comparison to a control group and pooled results found a mean difference of 2.22 kg in favour of the intervention group, but no consistent effects on markers of cardiovascular risk. The quality of the evidence was assessed as moderate. These interventions lasted 12, 52, and 104 weeks with no studies comparing effectiveness with different durations of treatment. Indirect comparisons across all 37 studies found no effect of duration of intervention on weight loss at 12 months. However, a previous systematic review and meta-analysis of direct comparisons between interventions of different lengths, mostly from controlled research studies, found that interventions providing 'extended care' led to 3.2 kg less weight regain than control interventions over a mean follow up period of 17.6 months following initial weight loss. An updated search of Pub Med and Scopus (to 12th January 2017) found no new direct comparisons of treatment duration.

Added value of this study

In a large randomised controlled trial in a sample broadly generalisable to the UK population, this trial finds that referral to a commercial programme for 12 weeks or 52 weeks produces greater weight loss than a brief self-help intervention. It extends previous findings by demonstrating that referral for 52 weeks achieves significantly greater weight loss than the standard 12-week referrals currently used in the UK National Health Service over 2 years. Contrary to common criticisms that these interventions could exacerbate health inequalities, there was no evidence that the outcome of treatment is moderated by socioeconomic factors such as gender, education and income. We also show, for the first time, that this extended referral achieves improvements in fasting glucose and glycosylated haemoglobin equivalent to more intensive health professional-led interventions. Using microsimulation modelling, we show for the first time that over a 25-year period the 12-week programme is cost-saving compared with a brief intervention, and that the 52-week programme is cost-effective compared with the 12-week programme.

Implications of all the available evidence

Referral to a commercial open-group behavioural weight loss programme for 12 weeks is an effective weight loss intervention and could be cost-saving for adults in the general population in the long term. Extending the referral length from 12 weeks (UK standard) to 52 weeks would significantly increase the clinical effectiveness of these programmes, by achieving greater weight loss and reductions in risk factors for diabetes and cardiovascular disease. While the 52-week programme is more expensive in the short term, in the longer term it would likely be cost-effective because of greater reductions in disease incidence.

Extended and standard duration weight loss referrals for adults in primary care (WRAP): a pragmatic randomised controlled trial.

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Contribution

ALA is the Chief Investigator. ALA, SAJ, PA, JCGH, MS, and SRC are grant holders. ALA and SAJ developed the research questions and designed the trial and PA, JCGH, MS, SRC, AM and AMT contributed to the design of the protocol. ALA, PA, JCGH, EJB, AMT, MT, JW, BRM, SAJ were responsible for data collection. JW and AT were the Trial Managers. DC was responsible for data management. GMW conducted the statistical analyses with input from AM. LI analysed the within-trial cost-effectiveness and attendance data with input from MS and DT. LP, LR, AJ, and LW conducted the microsimulation analyses. ALA, GMW, AM, PA, EJB, JCGH, SAJ, MS, LI, DT, LP, LR, LW, AJ contributed to the interpretation of data. ALA wrote the first draft of the manuscript. All authors contributed to the writing and critical revision of the manuscript.

Conflicts of Interest

ALA, SAJ, EJB, BRM and JCGH have received research funding to their institutions from Weight Watchers International and have given and received hospitality from providers of

1 commercial weight loss services on a small number of occasions. PA and SAJ have
2 conducted another publicly funded trial in which part of the intervention was delivered by
3 and donated free by Slimming World and Rosemary Conley, and they are principal
4 investigators on a trial funded through a grant to the University of Oxford from
5 Cambridge Weight Plan. JCGH is Principal Investigator on studies funded through
6 research grants to the University of Liverpool from the California Prune Board, Ingredion
7 and American Beverage Association (ABA), and has studentships funded through BBSRC
8 and ESRC with Unilever, Coca-Cola, and Tate & Lyle. JCGH provides expertise on health,
9 weight management and appetite control to the food and beverage, commercial weight
10 management, pharmaceutical and ingredient sectors.

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Summary

Background

There is good evidence that primary care referral to an open-group behavioural programme is an effective treatment for obesity, but little evidence on optimal treatment duration.

Methods

In this non-blinded parallel-group randomised controlled trial, we recruited participants (age ≥ 18 years, BMI ≥ 28 kg/m²) through 23 primary care practices in England. Participants were randomised using the study database in a 2:5:5 allocation to: brief weight loss intervention, a weight management programme (Weight Watchers®) for 12 weeks, or the same weight management programme for 52-weeks. We followed participants over two years. The primary outcome was weight at one year, analysed using mixed-effects models according to intention-to-treat principles adjusted for centre and baseline weight. In a hierarchical-closed-testing procedure we compared combined behavioural programme arms with brief intervention, then compared the 12-week and 52-week programmes. We conducted a within-trial cost-effectiveness analysis using person-level data and modelled outcomes over a 25-year horizon using microsimulation. Current Controlled Trials ISRCTN82857232.

Findings

Between 18th October 2012 and 10th February 2014, 1267 eligible participants were randomised to the brief intervention (211), 12-week programme (528) and 52-week programme (528). 823 (65%) completed an assessment at one year and 856 (68%) at two years. All participants were included in the analyses. At one year, mean weight change was -3.26 kg (brief intervention), -4.75 kg (12-week programme), and -6.76 kg (52-week programme). Participants in the behavioural programme lost more weight than those in the brief intervention [adjusted difference = -2.71 kg (95% CI -3.86, -1.55); $p < 0.0001$]. The 52-week programme was more effective than the 12-week programme [adjusted difference = -2.14 kg (95% CI -3.05, -1.22); $p < 0.0001$]. Differences between groups were still significant at two years. No adverse events related to the intervention were reported. Over two years, the incremental cost-effectiveness ratio (ICER; compared with brief intervention) was £159/kg lost for the 52-week programme and £91/kg for the 12-week programme. Modelled over 25 years after baseline, the ICER for the 12-week programme was dominant compared with the brief intervention. The ICER for the 52-week programme was cost-effective compared with the brief intervention (£2498/QALY) and the 12-week programme (£3804/QALY).

Interpretation

For adults with overweight or obesity, referral to this open-group behavioural weight loss programme for at least 12 weeks is more effective than brief advice and self-help materials. A 52-week programme produces greater weight loss and other clinical benefits than a 12-week programme and, although it costs more, modelling suggests it is cost-effective in the longer term.

Funding

- 1 This trial was funded by the National Prevention Research Initiative grant MR/J000493/1.
- 2 The cost of the Weight Watchers® programme and the costs of blood sampling and
- 3 analysis were funded by Weight Watchers International as part of an MRC Industrial
- 4 Collaboration Award.

BACKGROUND

The burden of disease attributable to excess weight places considerable strain on health care resources across the world.^{1,2} Behavioural weight management programmes are the first-line treatment for overweight and obesity, and although there is good evidence that some of these programmes can be effective, others are not.³ This may be due to differences in content and format of interventions, including the length of time support is provided. In the UK, the National Institute for Health and Care Excellence (NICE) public health guidance recommends that behavioural weight management programmes should last a minimum of 12 weeks⁴ and this is the standard length of the most commonly commissioned interventions.⁵ However, there is conflicting evidence about whether longer treatment duration would be more effective.^{6,7}

Open-group behavioural weight loss programmes are among the most commonly commissioned programmes in the UK and evidence suggests these programmes are effective and cost-effective.^{3,8} The current trial was designed to directly compare whether 52-week referral to an open-group weight management programme would achieve significantly greater weight loss and improvements in a range of secondary health outcomes than the current practice of 12-week referrals, and be more cost-effective.

METHODS

Study Design

This was a multi-centre, non-blinded, multi-arm parallel groups randomised controlled trial with imbalanced randomisation (2:5:5), conducted in England. The full protocol is described elsewhere.⁹

In brief, participants were recruited from 23 primary care practices across England between October 2012 and February 2014. Recruitment and follow up was conducted by three research centres: MRC Human Nutrition Research, Cambridge (coordinating centre), the University of Liverpool, and the University of Oxford. Cambridge and Liverpool teams recruited local practices and research staff conducted study visits at the research centre. Oxford recruited practices across southern and eastern England and practice staff (usually a research nurse) conducted study visits at the practice.

Ethical approval was received from NRES Committee East of England (12/EE/0363). This trial was registered at Current Controlled Trials ISRCTN85485463 on 12th October 2012.

Participants

Eligible participants (aged ≥ 18 years; body mass index (BMI) ≥ 28 kg/m²) were identified through practice records. Exclusion criteria were: planned (within two years) or current pregnancy; previous or planned bariatric surgery; currently following a structured, monitored weight-loss programme; participating in other research that could confound outcome measures; eating disorder; non-English speaking or with special communication needs. Practices could exclude additional patients they felt it was inappropriate to invite but were asked to report reasons. These additional exclusions included terminal illness/palliative care, dementia, a severe mental health problem or learning difficulty, carer for a terminally ill relative, or recently bereaved. Patients were invited by letter and asked to contact the local study coordinator for telephone screening if they were interested in participating. Eligible and willing participants were given an appointment, where a member of the research team weighed them and measured their height to confirm eligibility before randomisation. Where more than one household member was eligible and interested in participating, the first to enrol was taken as the participant. All participants gave written informed consent.

Randomisation and Masking

Participant details were entered into the trial database, which automatically assigned participants with a valid measured BMI to one of the three interventions (brief intervention, referral to the commercial open-group behavioural weight loss programme (behavioural programme) for 12 weeks, or referral to the same programme for 52 weeks) in a 2:5:5 allocation stratified by centre and gender, with a block size of 12. The randomisation sequence was generated by the trial statistician using Stata 12.1 and programmed into the database by the Data Manager. The sequence was unknown to research staff and participants. Once participants were enrolled and entered into the database, the database revealed the group allocation. Due to the nature of the intervention and the trial design, participants and research staff were not blinded to the intervention allocation after randomisation.

Procedures

Participants randomised to the behavioural programme were asked to attend a local Weight Watchers (WW) meeting once a week for the duration of their intervention (12 weeks or 52 weeks). At their baseline visit they were given a list of local meeting times and locations, a voucher booklet for 12 visits (the expiry date was set for 14 weeks from baseline) and a unique code to access digital tools for the duration of their intervention. Meeting vouchers were identical to those used in the National Health Service (NHS) referral schemes operating elsewhere in the country and allowed participants to attend meetings without charge. At the meeting, they gave the voucher to the group leader, but

1 were asked not to mention their participation in the trial to the group leader or other
2 members. Participants in the 52-week programme group were given a further three
3 books of vouchers when they returned for their 3 month visit (expiry date set for 54
4 weeks from baseline).

5 Participants allocated to the brief intervention were given a 32-page printed British Heart
6 Foundation booklet of self-help weight management strategies¹⁰ and research staff read
7 a scripted introduction that drew attention to each section of the booklet.

8 All participants attended measurement appointments at 0, 3, 12, and 24 months. Height
9 was measured to the nearest 0.1 cm using a stadiometer. Weight and fat mass were
10 measured to the nearest 0.1 kg using a 4-point Tanita segmental body composition
11 analyser. Waist circumference was measured to the nearest 0.1 cm using a tape
12 measure, half way between the lowest rib and the iliac crest. Blood pressure was
13 measured three times in a seated resting state using an automated blood pressure
14 monitor, and the mean calculated. Biochemical measurements were optional. Willing
15 participants were asked to give a fasting blood sample at 0 and 12 months for analysis
16 of glucose, glycosylated haemoglobin (HbA_{1c}) and lipid profile. All samples were analysed
17 in Cambridge using standardised methods (web appendix).

18 At each visit, participants self-reported their use of weight loss methods, including the
19 allocated intervention, and completed the EQ5D-3L^{11,12} as a measure of quality of life.
20 Data on health care resource use was also self-reported. Participants who were unable or
21 unwilling to attend a 12 month visit (primary outcome measurement) were asked to
22 provide a self-measured weight by phone or email. Self-reported weights are not
23 included in the primary outcome analysis but are included in a sensitivity analysis (web
24 appendix).

25 **Outcomes**

26 The primary outcome was change in body weight at 12 months. The secondary clinical
27 outcomes were: body weight at 3 and 24 months; proportion of participants losing $\geq 5\%$
28 body weight or $\geq 10\%$ of baseline body weight at 3, 12 and 24 months; waist
29 circumference, fat mass, and blood pressure at 3, 12 and 24 months; fasting blood
30 glucose, HbA_{1c}, triglycerides and HDL, LDL, and total cholesterol at 12 months; and self-
31 reported quality of life (EQ5D-3L) and health resource use at 3, 12 and 24 months. We
32 did not anticipate that adverse events related to the interventions would occur and so
33 did not formally record these.

34 **Statistical Analysis**

The sample size was calculated based on data from our previous trials^{13,14} with an expected difference of 2.3 kg between the brief intervention and combined behavioural programme groups, 1.3 kg difference between 12-week and 52-week programmes, and an assumed standard deviation of 6 kg. The hierarchical-closed-testing procedure compared the behavioural programme arms with brief intervention using a one-sided test and then, only if significant at the 5% level, conducted a two-sided test for a difference between 12-week and 52-week programmes in order to preserve a type I error rate of 5% without the need for a multiplicity correction. With a sample of 1200 participants allocated as 200 (brief intervention), 500 (12-week programme), and 500 (52-week programme), we had 99.95% power to detect a difference of 2.3 kg between brief intervention and the behavioural programmes, and 92.87% power to detect a difference of 1.3 kg between 12-week and 52-week programmes. The overall power of the study was 92.82%.

Analyses were pre-specified in the published protocol.⁹ The primary analyses evaluated differences between the intervention groups in mean weight change from baseline to 12 months. Given levels of attrition commonly encountered in weight-loss trials, four analysis approaches were taken to account for the impact of missing data: a missing at random (MAR) analysis using a variance components model; a completers only analysis; baseline observation carried forward (BOCF); and last observation carried forward (LOCF). For the MAR analysis, mean weight losses and their standard errors were obtained via a multiple imputation model using multivariate normal regression; 20 data sets for weight were imputed separately for each treatment group, with baseline weight, 3-month weight, 12-month weight, and 24-month weight regressed on centre. A model for multivariate normal data with baseline weight, 3-month weight, 12-month weight, 24-month weight as the outcome was fitted using measured weights at each time point via generalised least squares, with intervention group, visit, intervention group-by-visit interaction and centre included as fixed effects. For the completers only, BOCF and LOCF analyses, fixed effect models for continuous normal data were fitted to the 12-month weight data. The fixed effects were intervention group, centre and baseline weight. Analyses of secondary outcomes were conducted using the same regression based models. Data reported in the body of the paper used the MAR assumption. The web appendix contains analyses by all four methods. Sensitivity analyses were conducted to examine whether findings were sensitive to timing of the 12-month assessment or the inclusion of self-reported weights. All analyses were conducted using Stata 13.1.

A recent review highlighted the lack of evidence of this type of programme on socio-economic inequalities⁴, so we also conducted a post-hoc analysis of potential interactions

between intervention effects and gender, educational qualification and income. Coefficient estimates and their 95% confidence intervals were calculated for each fixed effect.

To establish within-trial cost-effectiveness over 24 months, we calculated the incremental cost-effectiveness ratio (ICER) as incremental cost per additional kg weight loss (see web appendix for full details). If the participant attended at least one session, the NHS would be charged a flat rate of £48.50 (12-week programme) or £190 (52-week programme). If they did not attend, there was no charge. Non-intervention NHS costs were estimated from health resource use questionnaires, which were completed by participants at baseline, 3, 12, and 24 months and were framed within a three months recall period.¹⁵ To ascertain the full NHS costs incurred over the 24 months follow-up period we applied area under the curve methods.¹⁶ A secondary analysis examined the ICER over a 1-year time horizon, to enable comparability with similar studies with shorter follow up.

We used the microsimulation model developed for the Foresight: Tackling Obesities project^{17,18} to estimate the effect of the three interventions on disease incidence, healthcare costs, quality adjusted life-years (QALY), and ICERs for 25 years following baseline (web appendix). This analysis used mean change in BMI for each intervention at 1 and 2 years, and assumed that between 2 and 5 years all participants returned to their baseline weight in a linear manner (i.e. regained all weight lost) and then followed national trends based on data derived from repeated cross-sectional samples in the Health Survey for England.¹⁹

The number of meetings attended by the participants in the behavioural programme groups between baseline and 3 months, 9 months and 12 months, and 21 months and 24 months, was self-reported. The proportion of participants who self-reported utilising other weight loss interventions was also calculated.

Data management was overseen by the coordinating centre's data manager. The data set linking treatment group to participant outcomes was only released to the investigators following completion of data collection for the primary outcome.

Role of the Funding Source

The funders of the study had no role in the design, data collection, data analysis, data interpretation, or writing of the report. ALA and GMW had full access to all data and ALA had final responsibility for the decision to submit for publication.

RESULTS

Between 18th October 2012 and 10th February 2014, 1954 participants were screened and 1269 were eligible and agreed to randomisation (Figure 1). Shortly after the baseline appointment, two enrolled participants were excluded because their GP reported illnesses that would have excluded them. These participants were removed and the remaining 1267 participants were included in the primary analyses. Data on participants who died during the trial is included up until the event. The number of participants completing each assessment was 1004 (79%) at 3 months, 823 (65%) at 12-months assessment, and 856 (68%) at 24-months. Using Pearson's chi-squared test, there was a borderline statistically significant association between the percentage of participants attending the 12-month appointment and intervention group ($p=0.0475$), though there was little evidence to suggest such an association for participants completing the 24-month assessment ($p=0.21$). Examination of the effect of individual characteristics on attendance by intervention group found no statistical evidence of bias in attendance over the study's duration. Analyses of biochemical risk factors are based on 837 participants (66%) who provided a blood sample at baseline.

Table 1 shows baseline characteristics by intervention group. Participants had a mean BMI of 34.5 kg/m^2 (SD 5.2), a mean age of 53.2 years (SD 13.8), 68% were female, 90% were White, 15% had diabetes, 50% had hypertension.

Figure 2 shows the weight trajectories of the three intervention groups at each time point using all measured weights. Mean (SE) weight change at 3 months was -2.04 kg (0.30) following brief intervention, -4.84 kg (0.21) in the 12-week programme, and -4.62 kg (0.18) in the 52-week programme. Participants in the combined behavioural programme arms lost more weight than those in the brief intervention [adjusted difference = -2.67 kg (95% CI $-3.28, -2.07$); $p < 0.0001$] and there was no significant difference between the 12-week and 52-week programmes [adjusted difference = 0.22 kg (95% CI $-0.26, 0.69$); $p = 0.371$]. Mean weight change at 12 months, the primary outcome, was -3.26 kg (0.68) in brief intervention, -4.75 kg (0.35) in the 12-week programme, and -6.76 kg (0.42) in the 52-week programme (Table 2). Participants in the combined behavioural programme arms lost significantly more weight at 12 months than those receiving a brief intervention [adjusted difference = -2.71 kg (95% CI $-3.86, -1.55$); $p < 0.0001$] and participants in the 52-week programme lost significantly more weight than those in the 12-week programme [adjusted difference = -2.14 kg (95% CI $-3.05, -1.22$); $p < 0.0001$]. On average, participants in all groups regained weight between 12 and 24 months but the differences between groups remained significant. Weight change between baseline and 24 months was -2.30 kg (0.73) in brief intervention, -3.00

kg (0.37) in the 12-week programme, and -4.29 kg (0.44) in the 52-week programme. Participants randomised to the behavioural programme lost significantly more weight than those receiving a brief intervention [adjusted difference = -1.44 kg (95% CI -2.87, -0.00); $p=0.0247$]. Participants randomised to the 52-week programme lost significantly more weight than those receiving the 12-week programme [adjusted difference = -1.32 kg (95% CI -2.46, -0.18); $p=0.0231$].

Participants randomised to the 12-week programme lost significantly more weight than the brief intervention group at 3 months [adjusted difference=-2.79kg (-3.44,-2.13); $p<0.0001$] and 12 months [adjusted difference=-1.61kg (-2.84, -0.38); $p=0.0105$] but there was no significant difference in weight loss between these groups at 24 months [adjusted difference = -0.74 kg (95% CI -2.45, 0.77); $p=0.338$].

Sensitivity analyses examining weight change with alternative assumptions about missing data gave similar results (web appendix). Research centre was not a significant predictor of weight change in any of the models. There was no evidence suggestion that the intervention effect differed by participant gender ($p=0.48$), educational attainment ($p=0.79$), or household income ($p=0.64$).

The percentage of participants losing $\geq 5\%$ and $\geq 10\%$ weight, and the relative risk between groups is shown in Table 3. At 12-month follow up, 57% of participants in the 52-week programme had lost $\geq 5\%$ of weight, compared with 42% in the 12-week programme and 25% in the brief intervention. Participants in the behavioural programme were significantly more likely than the brief intervention group to lose $\geq 5\%$ and $\geq 10\%$ body weight. Participants in the 52-week programme were significantly more likely than those in the 12-week programme to lose $\geq 5\%$ and $\geq 10\%$ weight.

At 12 and 24 months, participants in the 52-week programme had greater reductions in waist and fat mass than participants in the 12-week programme or brief intervention group (Table 4). At 12 months, participants in the 52-week programme had greater reductions in HbA_{1c} than those in the 12-week programme [adjusted difference=-1.31 mmol/mol (95% CI -2.47, -0.15); $p=0.0268$] and brief intervention [adjusted difference=-2.65 mmol/mol (95% CI -4.28, -1.01); $p=0.0015$] and greater reductions in fasting plasma glucose than those in the 12-week programme [adjusted difference=-0.29 mmol/L (95% CI -0.58, -0.00); $p=0.0497$] and brief intervention [adjusted difference=-0.46 mmol/L (95% CI -0.88,-0.03); $p=0.0342$]. There were no significant differences between the 12-week programme and brief intervention for either HbA_{1c} or fasting glucose. Changes over time in blood pressure, quality of life, triglycerides and

HDL, LDL and total cholesterol were small and there were no significant differences between groups. No participants reported adverse events related to the intervention.

Intervention usage is summarised in Table 5. At 3 months, 5% participants in the brief intervention group had attended a commercial weight management programme, compared with 68% in the 12-week programme and 69% in the 52-week programme. Only 1% of participants in all groups attended an NHS-led programme and less than 1% used weight-loss medication. For participants referred to the behavioural programmes, the mean number of sessions attended was 8.4 (SD 4.2) in the 12-week programme and 28.2 (SD 14.8) in the 52-week programme. Full details of the economic evaluation are in the web appendix. In brief, intervention costs, including GP referral time, are estimated as £18.50 (brief intervention), £60 (12-week programme) and £195 (52-week programme). There were no significant differences between groups in health care resource use per participant at baseline and throughout follow-up. The estimated incremental NHS cost per additional kg weight loss (expressed here as £/kg) was £91/kg for the 12-week programme and £159/kg for the 52-week programme. Analysis using a 1-year time horizon for consistency with other studies, reduced the ICER to £26/kg and £75/kg respectively.

The cost-effectiveness acceptability curve (CEAC, web appendix Figure A2) is based on weight loss at 2 years and includes all NHS costs incurred during that time. If decision-makers are willing to pay at least £60/kg, then the 12-week programme would be the preferred strategy. If decision-makers are willing to pay £200/kg, then the 52-week is the preferred strategy. If costs are restricted to intervention-only costs, the 52-week programme becomes the preferred strategy at £100/kg.

Microsimulation modelling estimated that over 25 years after the baseline year, the 12-week programme was cost-saving (dominant) compared with the brief intervention. The 52-week programme was cost-effective relative to both the brief intervention (ICER = £2498/QALY) and the 12-week programme (£3804/QALY).

In comparison to the brief intervention, the 12-week programme resulted in 623 fewer incident cases of disease, 643 additional QALYs, and a cost-saving of approximately £68,000 per 100,000 individuals. In comparison to the 12-week programme, the 52-week programme resulted in 1786 fewer incident cases of disease and generated 1282 additional QALYS, at a cost of approximately £4.9 million per 100,000 individuals. Further details are included in the web appendix.

DISCUSSION

Adults in primary care with overweight or obesity who were referred to an open-group behavioural weight management programme lost 2.7 kg (± 1.2) more weight at 1-year follow up than those who were given brief advice and self-help materials. Those who were referred to this behavioural programme for 52-weeks lost 2.1 kg (± 0.9) more weight than those who were referred for 12 weeks. Fifty-seven percent of participants referred to the 52-week programme lost more than 5% weight, compared with 42% referred to the 12-week programme and 25% of those in the brief intervention group. Five percent is often used as a cut-off for clinically significant weight loss, although even smaller weight losses are associated with improvements in markers of cardiovascular disease risk.²⁰ On average all groups regained some of the weight lost and at 2-years the difference in weight loss between the 12-week programme and the brief intervention was no longer significant, whereas the weight loss in the 52-week programme was significantly greater than both other groups. Participants in the 52-week programme also had larger reductions in waist circumference, fat mass, fasting glucose and HbA_{1c} than participants in the 12-week programme and the brief intervention. When the impact of the 12-week programme was modelled over 25 years, it was cost-saving compared with the brief intervention. Although the 52-week programme was more expensive in the within-trial analysis, when the impact was modelled over 25 years, it resulted in the greatest gain in QALYs and the greatest reduction in disease incidence. By standards set by the National Institute of Health and Care Excellence, the intervention is cost-effective in comparison to both the brief intervention and the 12-week programme. It should be noted that this assessment of cost-effectiveness does not include potential further savings in social care and indirect healthcare costs. It also uses a flat rate cost for each intervention, when in practice full costs would not be incurred if people did not complete the course, thus potentially overestimating intervention costs.

A strength of this trial is the large patient group that is broadly generalisable to the UK population. In our previous trial¹³, participants with a BMI 27-35 kg/m² were identified during routine consultations and recruited to the trial. The current trial was more inclusive (BMI 28-68 kg/m²) and participants were recruited by letter based on weight records. In the former, the mean BMI was 31.4 kg/m² whereas in the present study participants had a mean BMI of 34.5 kg/m², more comparable to the population typically referred to open-group behavioural programmes in NHS referral schemes.²¹ Mailing invitations to all eligible patients resulted in a higher proportion of male participants than seen in routine referral schemes,^{13,21} although this is still lower than the proportion of males in the UK population.²² More than half of participating practices were from areas with an index of multiple deprivation that is higher (more deprived) than the national

median and participants were drawn from a wide range of socioeconomic groups.²³ Most participants were white, with the proportion enrolled reflecting the ethnic make-up of the UK.²² There was no evidence that the intervention effects varied by gender or socioeconomic status. This is striking given oft-repeated views that these interventions are not appropriate for men and concerns that individual behavioural interventions exacerbate socio-economic inequalities in health.^{24 25} Taken together, the findings suggest that the intervention effects reported here may be generalisable to the UK adult population. Although uptake of the programmes by more deprived populations is somewhat lower than in less deprived areas²³, more targeted schemes, as have been implemented elsewhere¹⁴, might reduce health inequalities.

Loss to follow up at 1 year was slightly below average for weight loss trials,²⁶ and there was little attrition between 1 and 2 years. Three different intention-to-treat analyses were conducted that each make different assumptions about missing data, as well as two sensitivity analyses. The consistency of effects demonstrates the robustness of our findings. The pragmatic nature of the trial meant that participants in all groups were free to use other weight-loss methods during the trial. This reflects how these interventions are routinely delivered and allows direct translation of these findings to clinical practice. Only a tiny minority of participants in each arm used other NHS interventions or weight-loss medications, and only a small proportion of participants who were assigned to the brief intervention group went on to use a commercial weight loss programme. A strength of this trial is the 2-year follow up of participants, which gives important information on weight trajectories after treatment ends. The modelled cost-effectiveness over 25 years is based on assumptions about weight trajectories beyond 2 years, however we have been relatively conservative in these assumptions, assuming all weight lost is regained within 5 years. The within-trial ICERs are strongly affected by non-significant differences between groups in healthcare costs (highest in the 52-week programme and lowest in the 12-week programme) based on health-care usage data in 46.7% participants. However, sensitivity analyses (web appendix) provide information with which to assess the strength of these findings. Fasting status when blood was taken and attendance at Weight Watchers were self-reported and could be susceptible to reporting/recall bias. Reliance on subjects confirming that the blood sample was taken in a fasting state is a universal concern in any free-living study and findings related to glucose were congruent with findings for HbA_{1c}, which is not affected by fasting status. Attendance at Weight Watchers was self-reported and could be susceptible to reporting/recall bias. However, any bias in the attendance data does not impact the pre-specified outcomes which were conducted on an intention-to treat basis.

1 The weight losses seen in this study are consistent with previous trials of 12 weeks and
2 52 weeks referral to commercial open-group behavioural weight management
3 programmes, suggesting findings are robust.^{13,14,27} Estimates of the mean incremental
4 cost per additional kg lost for either duration of treatment are within the range of other
5 behavioural programmes (web appendix Table A4). The reductions in fasting glucose and
6 HbA_{1c} were not seen in our previous trial of the 52-week programme,²⁸ perhaps because
7 the lower baseline BMI and stricter inclusion criteria in that study meant that participants
8 had lower baseline values. Almost half of participants in the current trial had elevated
9 fasting glucose and/or HbA_{1c} at baseline. Reductions seen in the 52-week programme
10 participants at 12 months (-0.5 mmol/l fasting glucose and -2.8 mmol/mol HbA_{1c}) are
11 larger than those seen at the same timepoint in the intensive lifestyle intervention arm
12 of the Diabetes Prevention Programme (DPP; approximately -0.4 mmol/l fasting glucose
13 and -1 mmol/mol HbA_{1c})²⁹, whose participants were similar to those in the current study
14 in baseline BMI, HbA_{1c} and glucose and had similar weight loss at 12 months, but
15 achieved at a fraction of the cost.³⁰ Notwithstanding gradual weight regain and increase
16 in associated risk factors observed over 15 years follow-up, DPP achieved a 27%
17 reduction in the cumulative incidence of diabetes in the lifestyle intervention relative to
18 the control group.³¹ However the impact of these more scalable interventions on
19 diabetes incidence will depend on whether longer term weight trajectories are similar.

20 The programme we evaluated is widely available and participants in the brief
21 intervention group were neither encouraged nor discouraged from attending other
22 weight loss programmes. Only 1 in 20 chose to do so, compared with 14 in 20 of those
23 referred to these programmes. In the 12 week group, 19% of participants were still
24 attending the programme 12 months later at their own cost, compared with 9% of those
25 in the brief intervention. This suggests some legacy effect of the initial referral. However,
26 this is lower than the 42% of participants in the 52-week group who were still attending
27 at 12 months. As the median household income was about £30,000, it is likely that
28 many people would have been able to pay the cost of the programme (approximately
29 £5/week) suggesting it may be the act of referral itself that is the source of motivation
30 to attend, though it is impossible to exclude that lower attendance in other groups was
31 related to the cost. The importance of the referral is supported by qualitative data that
32 found the GP referral is perceived as an implicit recommendation of the programme and
33 the allocation of NHS resources to enabling their attendance increases motivation to
34 attend.³² It is also supported by another trial among people with obesity attending a GP
35 consultation unrelated to their weight, where 77% who agreed to participate in the trial
36 and were offered a referral to a weight management programme accepted it and 40%
37 attended.³³

The absolute weight loss among participants receiving only the brief intervention warrants consideration. Participants given 5 minutes of non-tailored advice and a self-help booklet lost over 3 kg at 12 months and over 2 kg at 24 months. Weight change in this group is larger than the average weight loss observed in a recent meta-analysis³ for interventions led by generalist primary care teams, and larger than the average weight loss seen in a systematic review of self-help interventions.³⁴ Given the small cost of this intervention (self-help booklet and three short appointments that could be delivered by a nurse or health care assistant), observational data would support the implementation of this intervention as a minimal standard in primary care. However, this finding highlights the importance of including a control group when evaluating weight loss interventions. A recent review has shown that control groups given minimal interventions will generally lose weight over the course of a trial.³⁵ In this review there was considerable heterogeneity in the absolute weight loss of control groups, which may reflect differences in study populations and trial design. The current trial illustrates this showing 3.4 kg weight loss in a minimal contact control group, when an almost identical brief intervention achieved less than 1 kg weight loss when used as a control group in a different population and context.³⁶

This trial demonstrates that referral to this commercial open-group behavioural weight loss programme increases weight loss relative to a brief intervention in primary care. Increasing the duration of the programme from 12 weeks to 52 weeks increases weight loss and improvements in other markers of diabetes and cardiovascular risk, most notably glycosylated haemoglobin and fasting glucose. Economic evaluation of this trial found that while the 52-week programme requires greater initial investment, it is likely cost-effective in the longer-term and commissioners should consider a move towards extended referral schemes.

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Research in context panel

Evidence before this study

A systematic review and meta-analysis conducted in November 2012 synthesised data from 37 trials of behavioural weight management programmes delivered in a context that could be replicated in routine clinical practice. Three studies evaluated primary care referral to a commercial open-group programme in comparison to a control group and pooled results found a mean difference of 2.22 kg in favour of the intervention group, but no consistent effects on markers of cardiovascular risk. The quality of the evidence was assessed as moderate. These interventions lasted 12, 52, and 104 weeks with no studies comparing effectiveness with different durations of treatment. Indirect comparisons across all 37 studies found no effect of duration of intervention on weight loss at 12 months. However, a previous systematic review and meta-analysis of direct comparisons between interventions of different lengths, mostly from controlled research studies, found that interventions providing 'extended care' led to 3.2 kg less weight regain than control interventions over a mean follow up period of 17.6 months following initial weight loss. An updated search of Pub Med and Scopus (to 12th January 2017) found no new direct comparisons of treatment duration.

Added value of this study

In a large randomised controlled trial in a sample broadly generalisable to the UK population, this trial finds that referral to a commercial programme for 12 weeks or 52 weeks produces greater weight loss than a brief self-help intervention. It extends previous findings by demonstrating that referral for 52 weeks achieves significantly greater weight loss than the standard 12-week referrals currently used in the UK National Health Service over 2 years. Contrary to common criticisms that these interventions could exacerbate health inequalities, there was no evidence that the outcome of treatment is moderated by socioeconomic factors such as gender, education and income. We also show, for the first time, that this extended referral achieves improvements in fasting glucose and glycosylated haemoglobin equivalent to more intensive health professional-led interventions. Using microsimulation modelling, we show for the first time that over a 25-year period the 12-week programme is cost-saving compared with a brief intervention, and that the 52-week programme is cost-effective compared with the 12-week programme.

Implications of all the available evidence

Referral to a commercial open-group behavioural weight loss programme for 12 weeks is an effective weight loss intervention and could be cost-saving for adults in the general population in the long term. Extending the referral length from 12 weeks (UK standard) to 52 weeks would significantly increase the clinical effectiveness of these programmes, by achieving greater weight loss and reductions in risk factors for diabetes and cardiovascular disease. While the 52-week programme is more expensive in the short term, in the longer term it would likely be cost-effective because of greater reductions in disease incidence.

Figure 1: Trial Profile

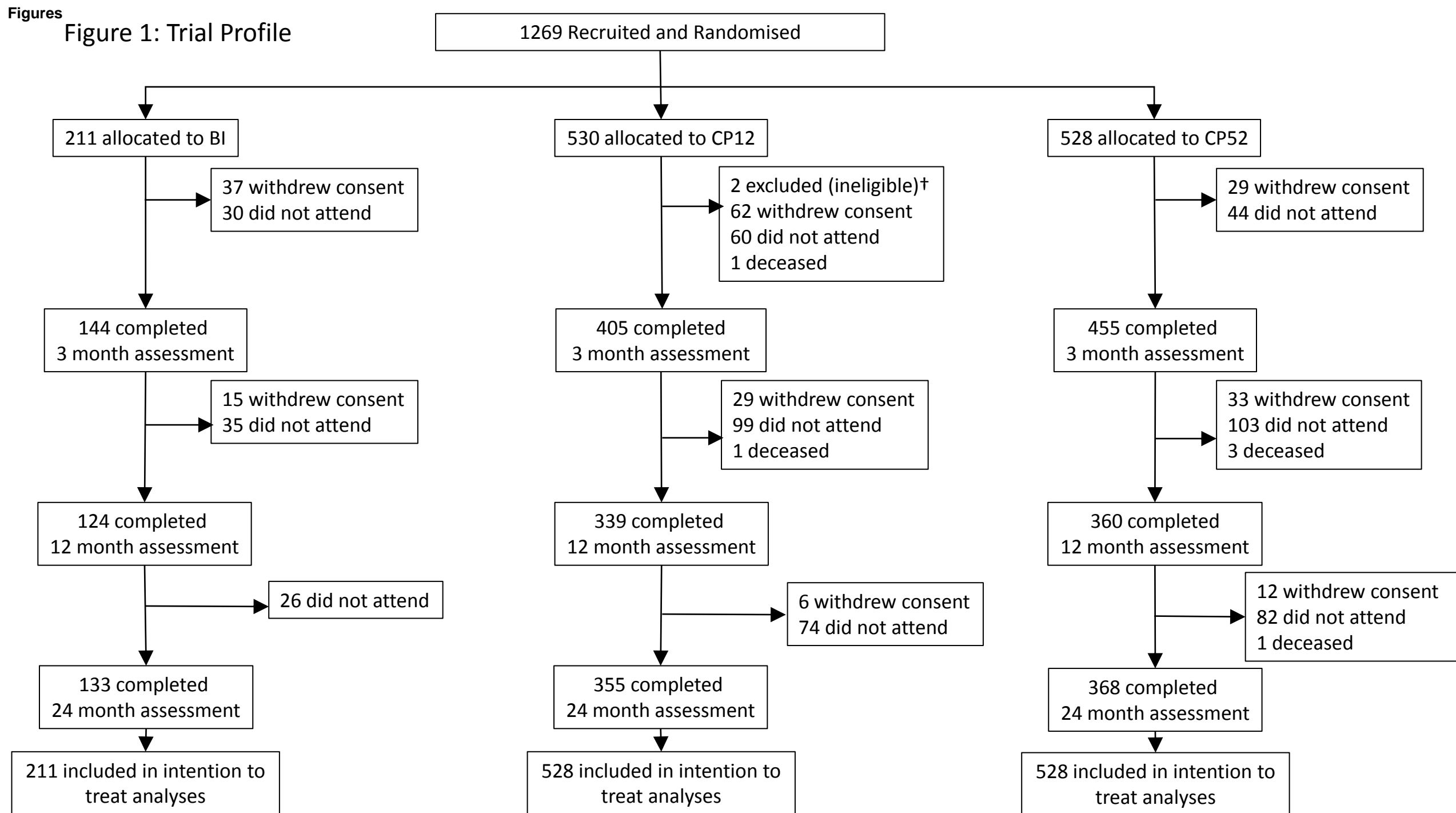


Figure 2: Weight change (SE bars) over time by intervention group, showing mean of all measured weights at each time point

No. Participants

Brief Intervention	211	144	124	133
12-week Prog	528	405	339	355
52-week Prog	528	455	360	368

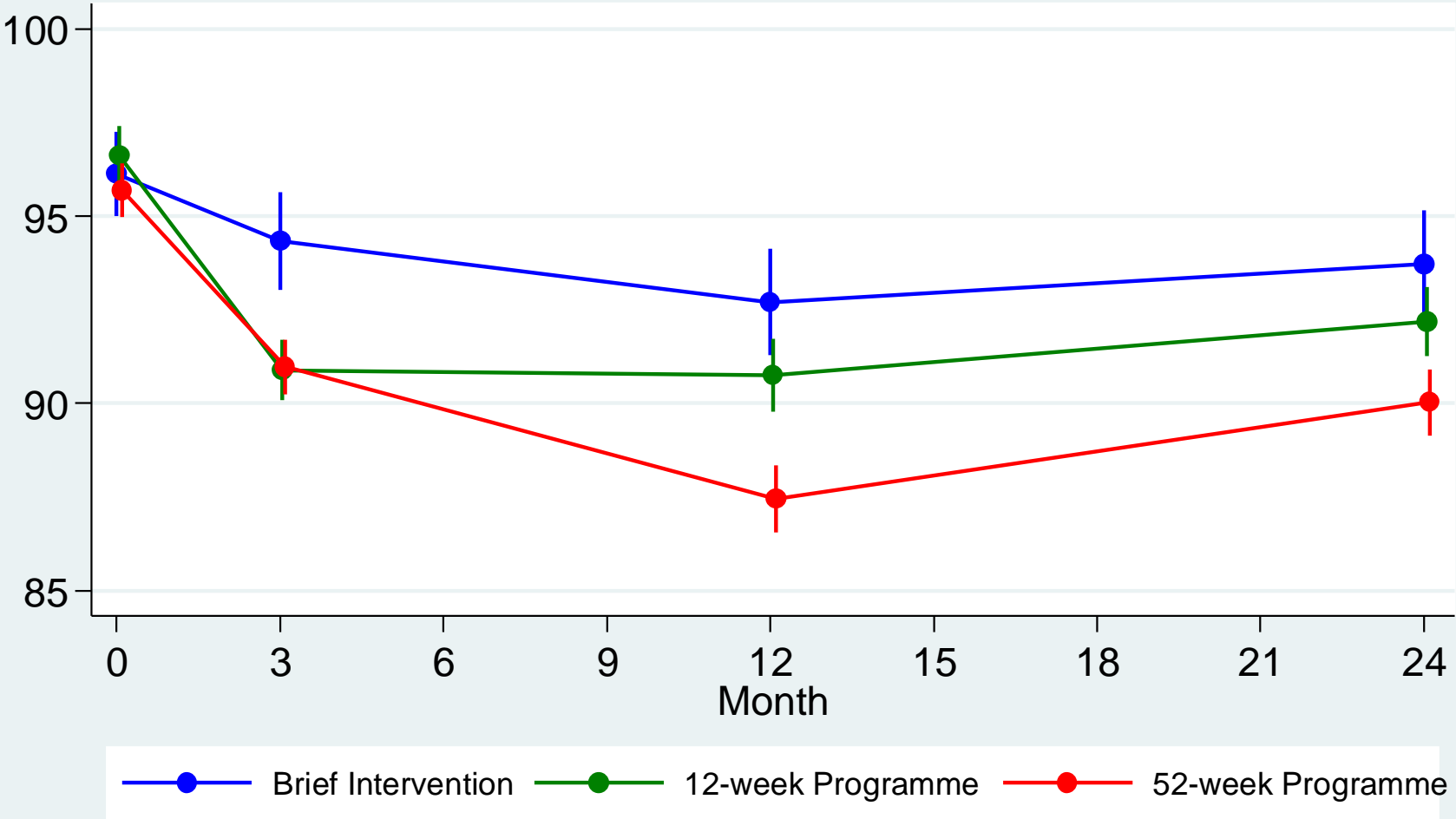


Table 1: Baseline characteristics of participants by intervention group

	Brief Intervention (N=211)		12-week Programme (N=528)		52-week Programme (N=528)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Age (years)	211	51.9 (14.1)	528	53.6 (13.3)	528	53.3 (14.0)
Weight (kg)	211	96.1 (16.4)	528	96.6 (17.9)	528	95.7 (16.4)
Height (cm)	211	167 (9.5)	528	167 (8.9)	528	167 (9.0)
BMI (kg/m ²)	211	34.4 (4.6)	528	34.7 (5.4)	528	34.5 (5.1)
Fat Mass (kg)	204	39.2 (9.9)	515	39.6 (11.8)	517	39.4 (11.1)
Waist (cm)	210	110 (11.9)	528	111 (12.4)	528	110 (12.7)
Systolic Blood Pressure (mmHg)	210	130.6 (15.7)	526	133.5 (17.2)	527	133.3 (18.1)
Diastolic Blood Pressure (mmHg)	210	79.7 (9.2)	526	80.7 (9.7)	527	79.9 (10.0)
Fasting Glucose (mmol/L)	134	5.8 (1.9)	345	5.6 (1.6)	326	5.8 (1.8)
HbA1c (mmol/mol)	143	41.9 (11.2)	354	40.9 (9.8)	338	41.7 (10.4)
Triglycerides (mmol/L)	146	1.6 (0.9)	357	1.6 (0.8)	339	1.5 (0.7)
Cholesterol (mmol/L)	146	5.5 (1.2)	357	5.3 (1.1)	337	5.3 (1.1)
LDL Cholesterol (mmol/L)	145	3.1 (1.2)	353	3.0 (1.0)	339	2.9 (1.0)
HDL Cholesterol (mmol/L)	146	1.6 (0.6)	357	1.6 (0.6)	339	1.7 (0.6)
Quality of Life (EQ5D-3L tariff)	197	0.786 (0.266)	508	0.783 (0.249)	504	0.793 (0.249)
Quality of Life (EQ-Vas)	201	70.3 (18.9)	515	70.9 (18.0)	506	70.0 (19.9)
	N (%)		N (%)		N (%)	
Sex						
Female		143 (68)		357 (68)		359 (68)
Male		68 (32)		171 (32)		169 (32)
Gross Household Income pa						
<£20,000		65 (31)		125 (24)		138 (26)
£20,000 - £39,999		56 (27)		132 (25)		137 (26)
≥£40,000		51 (24)		132 (25)		123 (23)
Missing/Prefer not to say		39 (18)		139 (26)		130 (25)
Ethnicity						
Asian/Asian British		9 (4)		11 (2)		15 (3)
Black/Black British		5 (2)		12 (2)		6 (1)
Mixed/Multiple Ethnic Group		4 (2)		4 (1)		7 (1)
White/White British		181 (86)		480 (91)		475 (90)
Other		2 (1)		6 (1)		7 (1)
Missing/Prefer not to say		10 (5)		15 (3)		18 (3)
Education						
Higher Degree or equivalent		23 (11)		79 (15)		68 (13)
University Degree or equivalent		48 (23)		108 (20)		97 (18)
Post-secondary Education		10 (5)		14 (3)		10 (2)
A-Levels or equivalent		53 (25)		95 (18)		110 (21)
GCSEs or equivalent		55 (26)		153 (29)		155 (29)
None		7 (3)		25 (5)		27 (5)
Missing/Prefer not to say		15 (7)		54 (10)		60 (11)

Table 2: Changes in weight from baseline (mean, SE) at 3, 12, and 24 months by intervention group

	N	Intervention			Test 1 (One-sided)		Test 2 (Two-sided)	
		Brief Intervention	12-week Programme	52-week Programme	Adjusted Difference (95%CI)		Adjusted Difference (95%CI)	
					Behavioural Programme vs Brief Intervention	p-value	52-week Programme vs 12-week Programme	p-value
3 months	1267	-2.04 (0.30)	-4.84 (0.19)	-4.62(0.17)	-2.67 (-3.28, -2.07)	<0.0001	0.22 (-0.26, 0.69)	0.371
12 months	1267	-3.26 (0.68)	-4.75 (0.35)	-6.76 (0.42)	-2.71 (-3.86, -1.55)	<0.0001	-2.14 (-3.05, -1.22)	<0.0001
24 months	1267	-2.30 (0.73)	-3.00 (0.37)	-4.29 (0.44)	-1.44 (-2.87, -0.00)	0.0247	-1.32 (-2.46, -0.18)	0.0231

BP = Behavioural Programme; CP12 = 12 weeks commercial programme; CP52 = 52 weeks commercial programme

Missing at random analysis; uses 20 imputed data sets. Treatment effects obtained from mixed effects models with residuals structured as a first-order auto-regressive process stratified by treatment group.

Adjusted differences are shown between combined treatment groups (CP12 and CP52) and BI (Test 1) and CP52 versus CP12 (Test2)
Analyses are adjusted for baseline observation and centre

Table 3: Proportion of participants losing at least 5% and at least 10% baseline weight at 12 and 24 months by intervention, and Relative Risk for combined behavioural programmes versus brief intervention and for 52-week programme vs the 12-week programme.

		Brief Intervention %(SE)	12-week Programme %(SE)	52-week Programme %(SE)	Behavioural Programme vs Brief Intervention Relative Risk (95%CI) p-value		52-week Programme vs 12-week Programme Relative Risk (95%CI) p-value	
≥5% weight loss	12 months	25 (2.97)	42 (2.15)	57 (2.16)	2.01 (1.51, 2.67)	<0.0001	1.36 (1.14, 1.62)	0.0005
	24 months	22 (2.87)	27 (1.93)	39 (2.12)	1.47 (1.08, 1.99)	0.0131	1.44 (1.16, 1.78)	0.0009
≥10% weight loss	12 months	9 (2.02)	15 (1.56)	30 (2.00)	2.40 (1.52, 3.78)	0.0002	2.00 (1.53, 2.62)	<0.0001
	24 months	9 (1.93)	12 (1.43)	18 (1.69)	1.80 (1.11, 2.93)	0.0182	1.49 (1.09, 2.04)	0.0125

Table 4: Changes from baseline (mean, SE) in secondary outcomes at 3, 12 and 24 months by intervention and adjusted differences between each intervention

			Intervention		Adjusted Difference (95%CI)		Adjusted Difference (95%CI)		Adjusted Difference (95%CI)	
	N	Brief	12-week	52-week	52-week Programme	p-value	12-week Programme	p-value	52-week Programme	p-value
		Intervention	Programme	Programme	vs Brief Intervention		vs Brief Intervention		vs 12-week Programme	
3 month changes										
Waist (cm)	1266	-2.42 (0.49)	-4.66 (0.25)	-4.20 (0.25)	-1.78 (-2.71, -0.84)	0.0002	-2.32 (-3.25, -1.39)	<0.0001	0.54 (-0.08, 1.17)	0.089
Fat mass (kg)	1236	-1.59 (0.30)	-3.95 (0.18)	-3.50 (0.14)	-1.85 (-2.43, -1.27)	<0.0001	-2.31 (-2.90, -1.72)	<0.0001	0.46 (0.04, 0.88)	0.0324
Systolic BP (mmHg)	1263	-2.39 (1.01)	-5.50 (0.66)	-5.25 (0.61)	-2.82 (-5.11, -0.53)	0.0158	-3.32 (-5.66, -0.98)	0.0054	0.50 (-1.24, 2.25)	0.571
Diastolic BP (mmHg)	1263	-2.59 (0.65)	-4.27 (0.41)	-3.64 (0.37)	-1.02 (-2.47, 0.42)	0.164	-1.78 (-3.25, -0.31)	0.0174	0.76 (-0.32, 1.83)	0.166
Quality of Life (EQ5D-3L tariff)	1209	-0.011 (0.016)	0.012 (0.009)	0.002 (0.009)	0.011 (-0.026, 0.047)	0.562	0.023 (-0.013, 0.060)	0.214	-0.013 (-0.036, 0.011)	0.298
12 month changes										
Waist (cm)	1266	-3.18 (0.64)	-5.15 (0.43)	-7.28 (0.45)	-4.05 (-5.54, -2.56)	<0.0001	-2.12 (-3.59, -0.65)	0.0048	-1.93 (-3.01, -0.85)	0.0005
Fat mass (kg)	1236	-2.48 (0.55)	-3.71 (0.33)	-5.05 (0.35)	-2.84 (-3.91, -1.77)	<0.0001	-1.40 (-2.47, -0.33)	0.0102	-1.44 (-2.22, -0.66)	0.0003
Systolic BP (mmHg)	1263	-2.77 (1.16)	-3.36 (0.73)	-3.74 (0.87)	-1.04 (-3.64, 1.56)	0.433	-0.59 (-3.18, 2.01)	0.657	-0.45 (-2.49, 1.59)	0.664
Diastolic BP (mmHg)	1263	-1.64 (0.87)	-2.31 (0.43)	-2.71 (0.51)	-1.20 (-2.98, 0.58)	0.186	-0.75 (-2.52, 1.01)	0.403	-0.45 (-1.70, 0.80)	0.483
Fasting Glucose (mmol/L)	800	-0.11 (0.20)	-0.27 (0.10)	-0.54 (0.08)	-0.46 (-0.88, -0.03)	0.0342	-0.17 (-0.59, 0.26)	0.436	-0.29 (-0.58, -0.00)	0.0497
HbA _{1c} (mmol/mol)	835	0.15 (0.69)	-1.49 (0.37)	-2.77 (0.47)	-2.65 (-4.28, -1.01)	0.0015	-1.34 (-2.96, 0.29)	0.107	-1.31 (-2.47, -0.15)	0.0268
Triglycerides (mmol/L)	837	-0.14 (0.07)	-0.23 (0.05)	-0.26 (0.03)	-0.09 (-0.25, 0.07)	0.281	-0.06 (-0.22, 0.10)	0.451	-0.03 (-0.14, 0.09)	0.646
Cholesterol (mmol/L)	837	-0.31 (0.10)	-0.32 (0.05)	-0.36 (0.05)	-0.05 (-0.24, 0.14)	0.625	-0.01 (-0.20, 0.19)	0.938	-0.04 (-0.17, 0.09)	0.556
LDL cholesterol (mmol/L)	830	0.01 (0.10)	0.02 (0.05)	0.02 (0.05)	0.00 (-0.19, 0.19)	0.9996	-0.00 (-0.19,0.19)	0.976	0.00 ('-0.13, 0.14)	0.964
HDL Cholesterol (mmol/L)	837	-0.27 (0.04)	-0.24 (0.03)	-0.24 (0.03)	0.01 (-0.12, 0.13)	0.917	0.03 (-0.10, 0.15)	0.668	-0.02 (-0.11, 0.07)	0.641
Quality of Life (EQ5D-3L tariff)	1209	-0.014 (0.018)	0.009 (0.011)	-0.012 (0.011)	0.014 (-0.025, 0.054)	0.476	0.029 (-0.011, 0.069)	0.150	-0.015 (-0.044, 0.014)	0.323
24 month changes										
Waist (cm)	1266	-3.64 (0.72)	-4.36 (0.47)	-5.57 (0.45)	-1.98 (-3.56, -0.41)	0.0137	-0.72 (-2.27, 0.83)	0.365	-1.27 (-2.46, -0.07)	0.0384
Fat mass (kg)	1236	-2.24 (0.62)	-2.40 (0.32)	-3.38 (0.38)	-1.36 (-2.64, -0.08)	0.0375	-0.36 (-1.60, 0.88)	0.572	-1.00 (-1.94, -0.07)	0.0359
Systolic BP (mmHg)	1263	0.64 (1.13)	-0.85 (0.87)	-0.09 (0.78)	-0.52 (-3.07, 2.02)	0.687	-1.22 (-3.75, 1.31)	0.344	0.70 (-1.32, 2.71)	0.497
Diastolic BP (mmHg)	1263	-0.83 (0.79)	-1.29 (0.50)	-1.11 (0.50)	-0.22 (-1.97, 1.52)	0.803	-0.32 (-2.05, 1.40)	0.713	0.10 (-1.13, 1.34)	0.872
Quality of Life (EQ5D-3L tariff)	1209	-0.005 (0.018)	-0.015 (0.012)	-0.018 (0.011)	-0.014 (-0.052, 0.025)	0.486	-0.011 (-0.050, 0.028)	0.587	-0.003 (-0.032, 0.027)	0.843

Analyses adjusted for baseline observation and centre. Mean weight change analyses use 20 imputed data sets. Treatment effects obtained from mixed effects models with residuals structured as a first-order auto-regressive process stratified by treatment group

Table 5: Self-reported intervention usage in the previous three months, recorded at 3, 12, and 24 months

		3 month visit			12 month visit			24 month visit		
		BI	12W	52W	BI	12W	52W	BI	12W	52W
Attendance questionnaire returned	N	132	382	436	108	321	342	115	321	330
Attended ≥1 meeting of a commercial weight loss programme in last 3 months	N	7	259	300	10	60	143	14	44	57
	% of responders	5.3%	67.8%	68.8%	9.3%	18.7%	41.8%	12.2%	13.7%	17.3%
Attended ≥9 meetings of a commercial weight loss programme in last 3 months	N	3	199	216	8	47	100	7	25	38
	% of responders	2.3%	52.1%	49.5%	44.4%	14.6%	29.2	6.1%	7.8%	11.5%
Attended an NHS-led programme in last 3 months	N	1	4	5	2	3	2	4	1	2
	% of responders	0.8%	1.0%	1.1%	1.9%	0.9%	0.6%	3.5%	0.3%	0.6%
Used weight loss medication in last 3 months	N	0	1	2	0	0	1	1	0	1
	% of responders	0%	0.3%	0.5%	0%	0%	0.3%	0.9%	0%	0.3%

BI = Brief Intervention; 12W = 12-week programme; 52W = 52-week programme

Web Appendix

[Click here to download Web Appendix: WRAP Web Appendix R2.SUBMITTED CLEAN.docx](#)

Consort Checklist

[Click here to download Supplementary Material: WRAP CONSORT 2010 Checklist.doc](#)

STUDY PROTOCOL

Open Access

Weight loss referrals for adults in primary care (WRAP): protocol for a multi-centre randomised controlled trial comparing the clinical and cost-effectiveness of primary care referral to a commercial weight loss provider for 12 weeks, referral for 52 weeks, and a brief self-help intervention [ISRCTN82857232]

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Abstract

Background: Recent trials demonstrate the acceptability and short term efficacy of primary care referral to a commercial weight loss provider for weight management. Commissioners now need information on the optimal duration of intervention and the longer term outcomes and cost effectiveness of such treatment to give best value for money.

Methods/Design: This multicentre, randomised controlled trial with a parallel design will recruit 1200 overweight adults (BMI ≥ 28 kg/m²) through their primary care provider. They will be randomised in a 2:5:5 allocation to: Brief Intervention, Commercial Programme for 12 weeks, or Commercial Programme for 52 weeks. Participants will be followed up for two years, with assessments at 0, 3, 12 and 24 months. The sequential primary research questions are whether the CP interventions achieve significantly greater weight loss from baseline to 12 months than BI, and whether CP52 achieves significantly greater weight loss from baseline to 12 months than CP12. The primary outcomes will be an intention to treat analysis of between treatment differences in body weight at 12 months. Clinical effectiveness will be also be assessed by measures of weight, fat mass, and blood pressure at each time point and biochemical risk factors at 12 months. Self-report questionnaires will collect data on psychosocial factors associated with adherence, weight-loss and weight-loss maintenance. A within-trial and long-term cost-effectiveness analysis will be conducted from an NHS perspective. Qualitative methods will be used to examine the participant experience.

(Continued on next page)

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Discussion: The current trial compares the clinical and cost effectiveness of referral to a commercial provider with a brief intervention. This trial will specifically examine whether providing longer weight-loss treatment without altering content or intensity (12 months commercial referral vs. 12 weeks) leads to greater weight loss at one year and is sustained at 2 years. It will also evaluate the relative cost-effectiveness of the three interventions. This study has direct implications for primary care practice in the UK and will provide important information to inform the decisions of practitioners and commissioners about service provision.

Trial Registration: Current Controlled Trials ISRCTN82857232. Date registered: 15/10/2012.

Keywords: Obesity, Weight-loss, Primary care, Adults

Background

Obesity has trebled since the 1980s and globally, excess weight is estimated to account for 44% of diabetes, 23% of ischemic heart disease and 7-41% of some cancers [1]. There is good evidence that intensive lifestyle interventions can produce weight loss linked to clinically significant health benefits [2], but such specialist interventions are costly given the high prevalence of obesity. Interventions delivered in primary care can also be demanding in terms of staff resources, set up and training and participant weight loss is often less than 5% of initial weight [3,4]. In the UK, NICE recommends consideration of any intervention that meets best practice, including referral to commercial weight loss programmes [5]. Commercial programmes are usually delivered in large groups by lay people, and preliminary evidence suggests they may be more affordable than interventions led by health professionals, making weight loss initiatives available for more individuals [6,7].

A number of commercial weight loss providers currently operate referral schemes for Public Health and the National Health Service (NHS) in the UK, whereby commissioners can purchase 12 week referral packages at a reduced cost, which are provided at no cost to patients. Two randomised controlled trials conducted by members of the current research team have demonstrated the effectiveness of commercial referrals. Jolly et al. compared a number of 12 week weight loss interventions in Birmingham's Lighten Up service, including three commercial providers, to a control intervention (12 vouchers to attend a leisure centre) [8]. Twelve-month weight loss was significantly greater among participants referred to a commercial programme (Weight Watchers; WW) than control participants [-4.35 ± 6.9 kg vs -1.63 ± 6.0 kg; $p < 0.001$]. Jebb et al. [9] demonstrated that overweight and obese adults referred to this commercial programme by their primary care provider for 12 months lost twice as much weight as those who received standard care [-5.1 ± 6.1 kg vs 2.3 ± 4.2 kg; $p < 0.001$]. These findings suggest that referral to a commercial programme (CP) by a primary care provider is a clinically effective weight loss intervention over a one year period. However, limited data on participants who agreed to attend

further follow up suggests significant weight regain beyond programme end [10].

The NHS currently provides 12 week referrals to commercial programmes. There is conflicting evidence on whether providing longer treatment interventions could result in greater and more sustained weight loss. In one meta-analysis of studies providing 'extended care', participants receiving extended care had, on average, 3.2 kg less weight regain than controls over a mean follow up period of 17.6 months [11]. The reduced weight regain in the extended care intervention in studies with 6-12 month follow-up was at least 1.5 kg. However, in a recent review of behavioural weight management programmes, meta-regression of trials with longer and shorter programmes found no benefit of longer programmes up to 1 year [12]. Indirect comparisons from Jebb et al. and Jolly et al. suggest that 12 months CP (weight loss 5.1 kg) achieves greater loss than 12 weeks CP (weight loss 4.4 kg, assessed at 12 months). The difference is small, but participants in Jolly et al. were heavier and older than those in the Jebb et al., two factors associated with greater weight loss in an audit of the CP's NHS referral database [13] and an observational analysis of the routine Lighten Up service [14]. Thus we might anticipate the difference in weight loss after 12 or 52 weeks intervention in comparable groups to be greater than the comparison between these two studies. Moreover, further analysis of Jolly et al. suggests the apparent impact of the WW intervention may have been atypically high. In the two other commercial providers (Slimming World and Rosemary Conley), mean weight loss at 12 months was smaller than WW, yet a much larger comparison ($n = 3000$) of the three providers in the routine Lighten-Up referral service shows that mean self-reported weight loss at 1 year in those attending WW was very close to the mean weight loss across all providers [14]. Mean 12 month weight loss for the three CPs in Jolly et al. was 2.7 kg, giving an assumed difference of 1.36 kg between this and the 52 weeks intervention in Jebb et al. A formal RCT is needed to show whether the greater loss in the 12 month programme is due to the longer referral and the current trial will directly compare weight loss at 12 months for participants receiving 12 weeks referral (CP12) and 52 weeks referral (CP52).

Obesity is a chronic, relapsing condition and the sustainability of weight loss achieved in short term interventions cannot be assumed. There is currently no published data on 12 week commercial referral outcomes beyond 12 months. In the limited data from participants from Jebb et al., 12 months CP did lead to greater weight loss than standard care, but this difference was small and sensitive to assumptions about missing data [10]. We will therefore follow participants up for 24 months to examine whether any initial differences in weight loss are sustained in the longer term.

Careful consideration has been given to the most appropriate control intervention. Since in many cases, obesity remains untreated in primary care, a no-intervention control may be considered to reflect standard care. However, recognition of obesity by GPs as part of recruitment to the trial and appointments for outcome measurements may constitute an intervention in its own right and in a recent review even minimal intervention 'control' groups lost weight [12]. Where offered, weight management interventions in primary care vary considerably. Since this is not the focus of this trial it is important to have a standardised 'control' intervention. Inclusion of a brief intervention based on written self-help materials will allow us to control for the impact of the GP offering a weight loss intervention and trial participation on weight loss and allow some consideration of the relative contribution of engagement and follow-up versus the nature and content of the specific intervention provided.

For NHS commissioners, one of the most important questions is whether an intervention offers value for money and a rigorous evaluation of cost-effectiveness has been built into the trial. Data on treatment costs, health-care usage and quality of life [15] will enable us to model whether any additional weight loss achieved through the 52 week programme is worth the additional costs. Initially this will consider cost-effectiveness from the perspective of the NHS, within the period of the trial (i.e. 24 months). However, ultimately, we want to know whether the interventions are likely to lead to an increase in length and quality of life, and at what cost. It is not practical to conduct a prospective study with lifetime follow up to establish this. Instead we propose using a well-developed decision-analytic model to estimate the long term impact of weight loss on risks of chronic disease and hence quality adjusted life years (QALYs) and cost.

Qualitative data suggests neither participants nor practitioners view weight management services as a priority in primary care and that some resist the idea that it is a medical issue in and of itself [16]. Thus, by delivering the intervention outside of a medical context, a CP fits better with participants' own view of weight management. This study will examine participant experience in greater depth to explore the ways in which individuals

understand and make sense of the imperative to lose weight, and the values and tensions arising from the primary care- commercial provider relationship. It will also examine the extent to which the weekly weigh in and the sense of peer support are experienced to be key aspects of the CP and the extent to which these are felt to facilitate weight loss.

Interventions for weight management could potentially be improved by developing a greater understanding of the psychosocial factors that explain individual variation in adherence, weight loss and post-intervention weight maintenance. There is a particular lack of knowledge about how these factors change during weight loss and how they affect weight maintenance. The current study will use validated questionnaires to explore a number of psychosocial factors that have either demonstrated an association with attrition, weight loss, and maintenance of weight lost in previous studies, or represent constructs identified as potentially important predictors of weight loss maintenance in recent reviews [17-19]. We will examine how baseline differences in these factors affect weight trajectories, how these factors change during and following a weight loss intervention, and how changes are associated with changes in weight.

Objectives

Primary objectives

The primary research question is whether the CP interventions achieve significantly greater weight loss from baseline to 12 months than BI, and whether CP52 achieves significantly greater weight loss from baseline to 12 months than CP12.

Secondary objectives

Clinical effectiveness

We will examine differences between the three interventions in weight, waist circumference, body composition, and blood pressure at 3, 12 and 24 months and differences in biochemical measures (blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and HbA1c) at 12 months. Specifically we will test the following hypotheses:

- i) Both CP interventions achieve significantly greater weight loss than BI from baseline to 3 months and baseline to 24 months and CP52 produces significantly greater weight loss than CP12 from baseline to 24 months.
- ii) Both CP interventions achieve significantly greater improvements in waist circumference, body composition and blood pressure than BI between baseline and 3, 12 and 24 months.
- iii) CP52 achieves significantly greater improvements in waist circumference, body composition and blood

pressure than CP12 between baseline and 3, 12 and 24 months.

- iv) Both CP interventions achieve significantly greater improvements in biochemical measures than BI between baseline and 12 months, and CP52 achieves significantly greater improvements than CP12.

Cost-effectiveness

We will examine the cost-effectiveness of each of these interventions. The following hypotheses will be tested:

- i. CP52 is more cost-effective than CP12, as assessed by both within trial cost effectiveness and long term cost-effectiveness analyses.
- ii. Both CP12 and CP52 are more cost-effective than BI.

Participant experience

A qualitative workstream will explore the attitudes of participants to primary care referrals to commercial providers for weight loss, and also their wider experiences of weight management. In line with a qualitative research methodology, the following three areas will act as a guide for the research that will also remain sensitive to the experiences and topics raised by participants:

- i) The extent to which participants feel that they have been referred for weight management in the NHS by their GP, and how this relates to their experience of participating in the programme and their attitudes toward weight loss.
- ii) The extent to which the weekly weigh in and the sense of peer support are experienced to be key aspects of the CP
- iii) The extent to which being 'overweight' or 'obese' is considered a medical issue by participants

Psychosocial factors

This study will also examine psychosocial factors that are associated with completion of the intervention, weight loss and weight loss maintenance, to enable greater understanding of who benefits from these interventions and to inform development of new interventions.

Biological sampling

This study will collect blood samples in order to examine changes in markers of risk of CVD and diabetes (fasting lipids, glucose and glycosylated haemoglobin). DNA will be collected for subsequent analyses of how genetic variation effects response to the interventions.

Method

Trial design

This is a multicentre, randomised controlled trial with a parallel design. Participants will be randomised to one of three interventions: Brief Intervention (BI), Commercial Programme for 12 weeks (CP12) or Commercial Programme for 52 weeks (CP52) in an allocation of 2:5:5 (Figure 1).

Population

Overweight and obese adults (BMI ≥ 28) in the UK, deemed eligible for weight management intervention by their general practitioner.

Setting

Participants will be recruited through primary care practices across England by three research centres. MRC Human Nutrition Research is the coordinating centre. They will recruit through local practices in Cambridgeshire and all measurements will be conducted by trained research staff at the research centre. The University of Liverpool will recruit through local practices across Merseyside and all measurements will be conducted by trained research staff at the research centre. The University of Oxford will recruit through practices across England and measurements will be conducted by trained health professionals (usually a research nurse) in the practice. Recruitment started in October 2012 and was completed in February 2014.

Participants

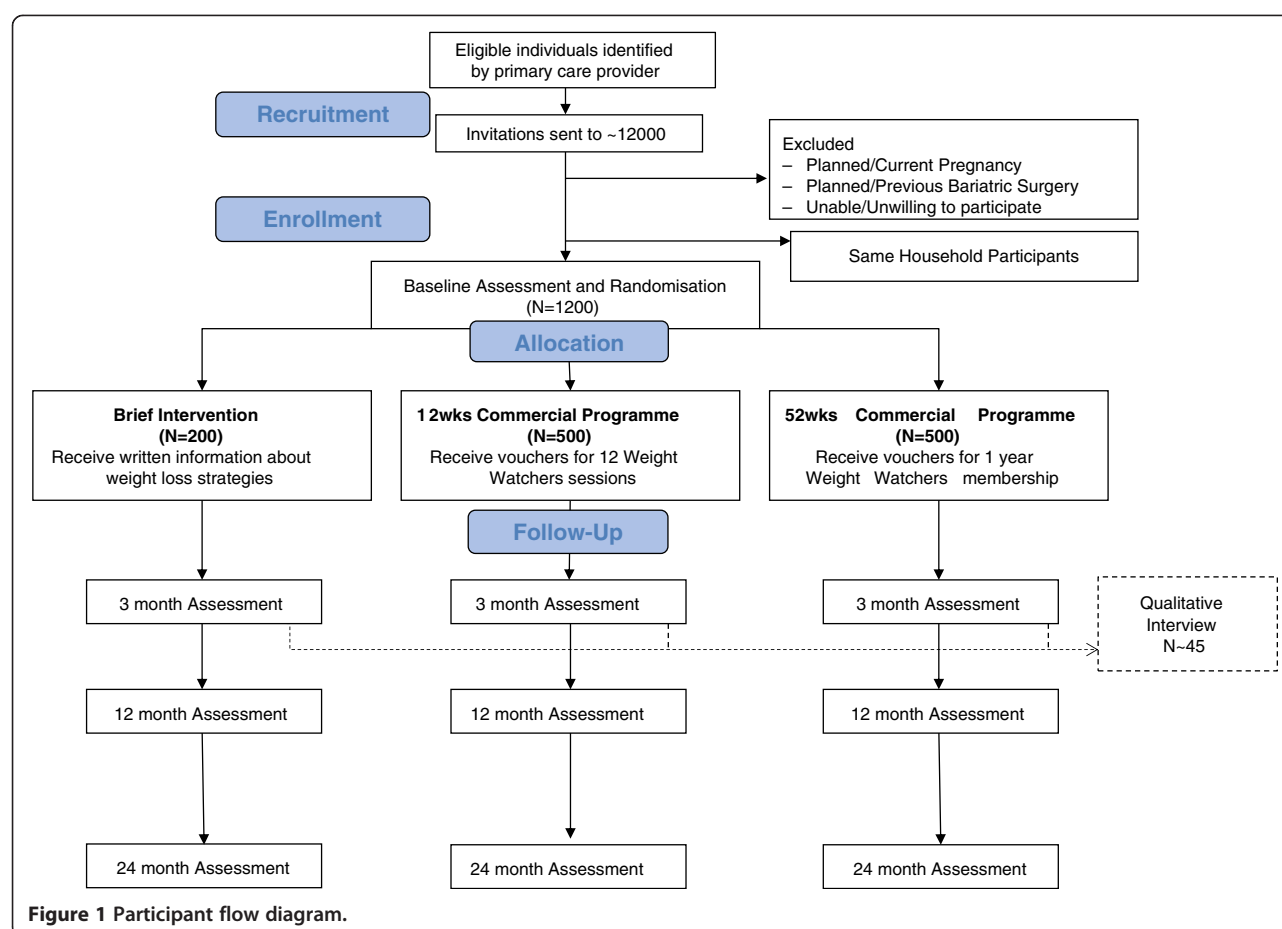
Participants will be 1200 overweight and obese adults in England, recruited by their local primary care provider.

Inclusion criteria

The inclusion criteria are BMI ≥ 28 kg/m², aged ≥ 18 years, and willing and able to comply with the study procedures. For simplicity, we will not vary the BMI criteria by ethnic group.

Exclusion criteria

The exclusion criteria are: planned or current pregnancy in the next two years; previous or planned bariatric surgery; currently following a weight-loss programme (defined as a structured, prescribed and monitored programme and not a self-regulated diet); non-English Speaking or with Special Communication needs that would preclude them from understanding the study materials and interventions. GPs will exclude patients who are inappropriate to invite into the study, for example patients who are violent/terminally ill/ have a history of an eating disorder. GPs will also be allowed to define any additional inclusion/exclusion criteria to meet local practice and will be asked to provide details on these for the reporting of the study. No further criteria



will be imposed, thus capturing the population that would typically be referred to these treatments. Participants receiving other weight loss treatments, e.g. Orlistat, will not be excluded as such participants would still be eligible for commercial referrals in standard practice, but this will be adjusted for in the analyses. Participants will be randomised to intervention arms, and thus those receiving additional treatment should be evenly spread across the interventions and these treatments will be accounted for in the cost-effectiveness analyses.

Inclusion of same household partners

Where more than one individual from a household is eligible and wants to enrol in the study, both members of the household will be allocated to the same treatment group (randomising participants at the household rather than the individual level) but only one person per household (the first to enrol) will be enrolled as a 'participant' who will provide measurements for the trial and attend follow-up visits. The 'non-participant' member(s) of a household will be referred to as 'same household partner', and will attend a 'baseline' visit to give consent and to receive their intervention materials. The 'same household partner' will be asked for consent to obtain their

attendance and weight data from Weight Watchers (if they are allocated to this arm) through their WW NHS Referral Database. There is also potential for participants to be part of a household where other members are engaged in weight loss programmes, outside of this study. Therefore, all participants will be asked to provide information about weight loss activities within their household, regardless of whether they have a partner in the study or not.

Recruitment

GP practices will be identified and recruited by the local Primary Care Research Network (PCRN). Practices will be targeted that do not have an existing contract with commercial weight loss services. In this way participants allocated to the brief intervention will not be denied standard care.

Based on the 10% recruitment rate from Jolly et al., we will approach approximately 12000 eligible individuals to recruit 1200 participants. The primary care provider will search their electronic registers for eligible individuals and GPs will screen out those to whom it would be inappropriate to send a letter (for example patients known to have a history of eating disorders or to be terminally

ill). The letter will not mention the participant's weight, but offers the availability of weight management and also will give brief details of the trial. Interested participants will be asked to telephone (on a designated Freephone number) or email the study co-ordinator at their local site for further information. A member of the research team will then describe the trial to the potential participant, undertake further screening, and, if agreeable, offer an appointment for baseline assessment and enrolment in the trial. This will be confirmed by letter, accompanied by a participant information sheet.

We will monitor uptake of the trial by ethnic group and by gender. GPs will be asked in their search for eligible participants to report summary statistics of the gender and ethnic composition of the eligible population. By comparing the recruited population to the eligible population we will be able to examine whether take-up of referral differed by ethnicity or gender.

Randomisation

At the first assessment, a member of the research team trained in taking informed consent will ensure that the participant understands the trial and has read the participant information sheet. They will confirm their eligibility for the study and obtain written consent for their participation in the trial. Participant details, including baseline weight, will be entered into an online database by a member of the research team.

The database will automatically assign participants with a valid recorded baseline weight to one of three interventions (BI, CP12, CP52). The randomisation sequence was generated by the trial statistician and allocates participants in a 2:5:5 allocation stratified by centre and gender, with a block size of 12. The sequence is unknown to research staff and participants.

Due to the nature of the intervention and the trial design, neither participants nor research staff will be blinded to the intervention allocation.

Withdrawal

Participants are free to withdraw from the trial at any time, without this affecting their care, by informing a member of the research team. Participants who withdraw will not be replaced, and data already collected will be used unless the participant requests that it be removed.

Participants might choose not to attend the commercial weight loss programme, or may stop attending sessions during the trial. Participants who withdraw from the intervention will be followed up at assessment appointments in the same way as other participants unless they also choose to withdraw from the trial.

Three contact attempts (by different means and at different times) will be made for each follow up appointment. On the third attempt to schedule an appointment,

or where a participant informs us that they are unable or unwilling to attend a follow up appointment, a self-measured weight will be requested. These data will not be included in the primary analyses but will provide additional data that can be used for sensitivity analyses where it is considered appropriate.

Interventions

Referral to a commercial provider

Participants who are assigned to the two commercial referral arms will receive vouchers to attend Weight Watchers sessions and asked to attend a local meeting that is convenient for them. They will be asked not to mention their participation in the trial to the group leader or other members, to make their experience as representative as possible.

CP12: Participants allocated to the 12 week referral will receive free vouchers to attend 12 Weight Watchers sessions and access to their internet resources for 16 weeks. This is the package currently used in the WW NHS Referral Scheme and currently costs the NHS £55 + VAT.

CP52: Participants allocated to the 52 week referral will receive free vouchers to attend 52 sessions of Weight Watchers and access to their internet resources for 12 months. This package is estimated to cost the NHS £190 + VAT.

Brief intervention

The control intervention is a standardised brief intervention: recognition of the problem by the GP (letter of invitation), basic written information on self-help weight loss strategies provided by a member of the research team at the baseline visit (British Heart Foundation Booklet: So you want to lose weight... for good) and weighing at follow up (coincides with outcome measurements at 3, 12 and 24 months).

Adherence

Attendance at CP meetings will be monitored both through self-report at assessment appointments and data collected by WW at weekly meetings (which can be provided, with consent, through the WW NHS referral database and tracked using NHS referral ID) and these data will be controlled for in sensitivity analyses. Similar information may be available from WW regarding website usage, and this data will be combined with that collected via self-report. We will also collect self-report data on the extent to which BI participants have used their self-help materials.

Outcomes

Clinical effectiveness outcomes

The primary outcome will be body weight (kg) at 12 months. Secondary clinical outcomes will be: body

weight (kg) at 3 and 24 months, whether a participant has lost $\geq 5\%$ and $\geq 10\%$ of initial body weight at 3, 12 and 24 months; waist circumference, body composition, and blood pressure at 3, 12 and 24 months; blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and HbA1c at 12 months.

Cost-effectiveness outcomes

The incremental cost-effectiveness ratio (ICER) of the intervention is the main outcome of the economic evaluation and will be expressed as incremental costs per incremental change in weight/BMI for the within-trial evaluation.

Adverse events

This is a low risk trial with little reason to consider that adverse events would arise as a result of following any one of the interventions. Accordingly no formal adverse event monitoring is planned.

Visits and measurements

Participants will attend measurement appointments at 0, 3, 12 and 24 months. Details of which measures will be taken at which appointments are summarised in Table 1.

Clinical measurements

All clinical measurements will be made in line with standardised operating procedures by trained research staff. Participants will be asked to remove shoes and heavy clothing items. Height (cm) will be measured in cm using a stadiometer. Weight and fat mass will be measured in kg using a Tanita segmental body composition analyser. Waist circumference (cm) will be measured using a tape measure, half way between the lowest rib and the iliac crest. Blood pressure will be measured using standardised methods.

Biochemical measurements

Biochemical measurements are optional for participants and taken under separate consent. Blood samples will be

Table 1 Schedule of enrolment, interventions, and assessments

TIMEPOINT	STUDY PERIOD				
	Enrollment	Baseline visit	Post allocation		Close-out
	-t ₁	0	3 months	12 months	24 months
ENROLMENT:					
Eligibility screen	X	X			
Informed consent		X			
Allocation		X			
INTERVENTIONS:					
Brief Intervention		X			
12 weeks Commercial Programme		X	X		
52 weeks Commercial Programme		X	X	X	
ASSESSMENTS:					
Height		X			
Weight		X	X	X	X
Fat mass		X	X	X	X
Waist Circumference		X	X	X	X
Blood Pressure		X	X	X	X
Blood Glucose		X		X	
Lipid Profile		X		X	
HbA1c		X		X	
DNA		X			
Demographics Questionnaire		X	X	X	X
Health Care Usage Questionnaire		X	X	X	X
EQ5D		X	X	X	X
Psychosocial Questionnaires		X	X	X	X
Intervention Usage Questionnaires		X	X	X	X
Qualitative Interviews (subset only)			X		

taken by fully trained research staff in line with standardised operating procedures. For assessment appointments where blood will be taken (0 and 12 months), participants will be asked to attend in a fasted state (no food or drink for 12 hours prior to the appointment).

At baseline and 12 months, participants will provide a sample of whole blood for analysis of glucose, glycosylated haemoglobin (HbA1c) and lipid profile. At baseline, an additional sample of whole blood will be collected in an EDTA tube, frozen at -80 and stored for later extraction of DNA and outside the trial protocol.

Health care usage measures

At each visit, participants will complete a Health Care Usage Questionnaire to assess their use of Health Care Services in the last 3 months.

Psychosocial measures

Participants will complete a series of questionnaires at or before each assessment to assess psychosocial factors related to weight control.

The Flexible and Rigid subscales of the Eating Inventory [20] measure cognitive dietary restraint and distinguish flexible and rigid dietary restraint strategies.

The Power of Food Scale (PFS) [21] measures individual differences in hedonic hunger (hunger in the absence of energy need).

A visual analogue scale (VAS) will be used to assess state hunger at the time the questionnaire is completed [22]. Sensitivity analyses can examine whether this influences responses to questionnaires about eating behaviour.

The Self-Report Habit Index (SRHI) [23] is a measure of behavioural frequency, automaticity and identity, which has also been used to measure the automaticity of thoughts, such as body-related cognitions. In the current study, we will use this measure to examine the extent to which “watching what I eat” and “exercising regularly” become automatic and are seen as part of a participant’s identity, and the extent to which this predicts weight loss and weight loss maintenance.

The Treatment Self-Regulation Questionnaire; Diet Self-Regulation Questionnaire (DSRQ) and Exercise Self-Regulation Questionnaire (ESRQ) measure the extent to which a participant’s motivation to participate in treatment, eat a healthy diet, or exercise, is autonomous (i.e. they are motivated by personal reasons) or controlled (i.e. they are motivated by perceived pressure from others).

The Problem Eating Behaviours Questionnaire (PEBQ) [24] measures the extent to which particular eating behaviours are problematic for participants.

The *EQ5D* [15] is a self-report measure of quality of life, which will be used to calculate QALYs for the cost-effectiveness analysis.

We will measure life satisfaction using the *Satisfaction with Life Questionnaire (SLQ)* [25] and depression and anxiety using the *Hospital Anxiety and Depression Scale (HADS)* [26].

Qualitative data collection

A subset of participants from the Cambridge centre will be recruited to participate in a qualitative study. Data will be collected through semi-structured interviews with up to 15 participants in each intervention. A maximum-variation (heterogeneity) sampling technique will be used to select potential interviewees based on demographic information obtained during the telephone screening questionnaire and through a questionnaire at the baseline visit. At the 3 month visit selected participants (including some who have dropped out of treatment but not withdrawn from follow-up) will be invited to participate in an interview. Participants will be offered the choice between having the interview at their home or in a private office at the University of Cambridge. Interviews will not be held where study procedures are conducted, to reduce associations between the interview and the measurement visits of the trial in order to encourage participant’s to speak openly about their experiences of the intervention to which they have been assigned. Interviews will last approximately one hour and will follow a general topic guide that will be piloted with a subset.

Statistical analysis

Analysis design

There is already good evidence to suggest that CP produces significantly greater weight loss than BI and in the event that CP is not better than BI then the comparison of the CP arms would not be of interest. Accordingly we will conduct a sequential analysis, which will preserve the Type 1 error of 5% without the need for a multiplicity correction such as Bonferroni. The sequential analysis will consist of the following 2 stages:

- i) Test the one-sided hypothesis that weight loss in the CP groups combined is greater than the weight loss in the BI arm.
- ii) If the first test is significant at the 5% significance level, then test the two-sided hypothesis that there is a difference between CP52 and CP12 weight loss at the 5% significance level.

Sample size calculation

We based the power calculation on data from our previous trials [8,9] with an expected difference of 2.3 kg between BI and combined CP, 1.3 kg difference between CP12 and CP52 (for example, a weight loss of 1.05 kg in the BI arm, 2.7 kg in the CP12 arm and 4.0 kg in the

CP52 arm), and an assumed standard deviation of 6 kg. The statistical testing will be performed sequentially firstly by comparing CP arms with BI and then only if significant to then test for a difference between CP12 and CP52. Power is optimised by allocating more participants to the CP arms where the smaller difference is expected. With a sample of 1200 participants allocated as 200 BI, 500 CP12 and 500 CP52, we will have 99.95% power for the first test, to detect a difference of 2.3 kg between BI and combined CP and 92.87% power to detect a difference of 1.3 kg between CP12 and CP52. The total power of the study will be 92.82%.

Clinical effectiveness

The primary analyses will assess differences in mean weight change from baseline to 12 months between the intervention groups. In order to investigate the impact of missing data, four analysis approaches will be taken: completers only, baseline observation carried forward (BOCF), last observation carried forward (LOCF) and a missing at random (MAR) analysis using a variance components model. For the LOCF, BOCF and completers analyses, fixed effect models for continuous normal data will be fitted to the 12 month weight data. The fixed effects will be intervention group, centre and baseline weight. For the MAR analysis, a model for multivariate normal data with the same fixed effects will be fitted using measured weights at each time point using generalised least squares. Coefficient estimates and their 95% confidence intervals will be calculated for each fixed effect.

All assumptions of the models will be checked using appropriate graphs (eq a Q-Q plot of residuals to check normality, residuals versus predicted values to check homogeneity of residual variance.) If the residuals are not normally distributed then the dependent variable may be transformed to normality, if there is no such transformation then non-parametric methods will be considered.

Secondary analyses will include analyses of weight change at 3 and 24 months; changes in blood pressure, waist circumference and fat mass at 3, 12 and 24 months; changes in biochemical measures at 12 months. These will be analysed using the same regression based models. Numbers of participants in each group achieving $\geq 5\%$ and $\geq 10\%$ weight loss at 12 and 24 months will also be explored.

Summary tables will be produced to look at the demographic distribution of the sample (age, sex, initial weight, BMI); attendance rates; time course of attendance; website usage.

Cost effectiveness

Within-trial cost-effectiveness

The incremental cost-effectiveness ratio of the intervention is the main outcome of the economic evaluation and will

be expressed as incremental costs per incremental change in weight/BMI for the within-trial evaluation. Cost items to be included will be the cost of the intervention (i.e. cost to NHS of referral packages and infrastructure related to the operation of the referral scheme), primary, secondary, and tertiary health care use associated with weight-related disease (especially diabetes, coronary heart disease, colon cancer, and musculo-skeletal disorders). At baseline, participants will complete a health care usage questionnaire covering health service attendances and any weight loss treatment for the previous 3 months. This questionnaire will be completed again at 3, 12 and 24 months. Analysis of uncertainty will be conducted with a non-parametric bootstrap of the sampled data to generate a cost-effectiveness acceptability curve showing the probability that the intervention is cost-effective at various willingness-to-pay thresholds per unit of outcome. The within-trial cost-effectiveness analysis will be conducted jointly with the outcome analysis in year 3 of the study. The data will also be incorporated into the economic model.

Long term cost-effectiveness

Measuring cost-effectiveness in terms of costs per QALYs will allow the intervention to be compared with many alternative uses of existing NHS budgets. We will use the UK Health Forum's "Obesity Micro-simulation Model". The estimates the future burden of diseases by making evidence based extrapolations of selected risk factors specific to the following BMI related diseases; currently hypertension and stroke, diabetes mellitus type 2, cardiovascular diseases including angina pectoris, myocardial infarction, musculo-skeletal disorders including osteoarthritis, low back pain and knee arthrosis; obesity associated cancers including colorectal, endometrial, ovarian, breast, cervical, prostate and possibly also gallbladder, pancreatic and renal. The micro-simulation incorporates a sophisticated economic module. The module employs Markov-type simulation of long-term health benefits, health care costs and cost-effectiveness of specified interventions. It synthesises and estimates evidence on cost-effectiveness analysis and cost-utility analysis within the countries. The model is used to project the differences in quality adjusted life years (QALYs), lifetime health-care costs and as a consequence of interventions incremental cost effectiveness ratios (ICERs). Sensitivity analysis is also done within this model. Outputs can be discounted for any specific discount rate.

Qualitative analysis

Audio recordings will be transcribed verbatim by an external agency, checked for accuracy and imported into NVivo, along with the original audio files. Basic descriptive variables will be imported from the main trial database to analyse the interview and diary data. Initial analysis using a limited set of codes drawn directly from

questions used in the topic guide will be conducted by at least two members of the team to ensure general reliability and appropriateness of categories. Analysis will then proceed iteratively in order to remain sensitive to the richness of data itself and develop a detailed hierarchy of emerging themes that address more implicit, and cross-cutting issues that emerge through the open-nature of the interviews. Exploiting the dynamic capacity of NVivo software, these themes will serve as the basis for comparison between participants. Analysis of the overall dataset will consequently enable both a narrative-based account of individual experiences, but also the extent to which they are intervention specific.

Discussion

With one quarter of adults defined as clinically obese, and with growing financial pressures on health services, this trial will provide important information on the use of commercial providers to deliver weight management services in partnership with health professionals. Findings will provide transparent information about treatment and outcomes and will enable formation of clear guidance for commissioners and referring practitioners.

Guidance for commissioners from the Department of Health in England currently recommends 12 week interventions. While there is some evidence that longer interventions might improve weight loss, this evidence is inconsistent and generally comes from indirect comparisons between studies. Changing current practice to include longer referrals would require evidence of both greater clinical effectiveness and cost-effectiveness at a population level.

While the quantitative data in this study can provide guidance on the clinical and cost-effectiveness of the treatment, qualitative data will elucidate some key issues surrounding commercial partnerships, in particular patient perceptions regarding the acceptability of these interventions. This data will also provide insight into what participants perceive are the active ingredients of these interventions and what patients want weight management services to provide.

Data on psychosocial factors can be used to identify inter-individual differences in weight trajectories and could potentially be used to assist in stratifying patients to treatments likely to be effective. Data on changes in these factors during and following the intervention, and their association with weight trajectories, could potentially be used to inform improvements in existing interventions and the development of new interventions.

This trial endeavours to evaluate how effective this intervention would be in routine clinical practice, rather than under optimal controlled conditions. However, the conditions of this trial differ somewhat from those of routine clinical practice. Firstly, participants are recruited

by letter and all participants who meet inclusion criteria and are invited. Thus our sample may be more heterogeneous than those who a GP refers following a face-to-face consultation. Secondly, in two of the research centres, participants attend a research centre for their initial intervention allocation and all assessments. This enables greater control over data quality and participant follow-up, but differs from how the intervention would be rolled out in primary care.

Weight loss studies are notorious for high attrition, which can compromise the analysis and interpretation of data. While every effort will be made to enable participants to attend follow up assessments, continued participation in the trial is voluntary and we anticipate that there will be a substantial number of people who do not complete all measurements. However, this also reflects what would happen in clinical practice where many participants will not follow the programme they are referred to, or may not return for follow-up. Data will be analysed on an intention to treat basis. While no method of analysis is without limitations, this should give the best estimation of population level effectiveness.

Research governance

Ethical approval

This is version 2.9 of the trial protocol dated 28th July 2013. The Medical Research Council is the sponsor of the trial. This trial was registered at current controlled trials ISRCTN85485463 on 12th October 2012. Ethical approval was received from NRES Committee East of England - Cambridge East (12/EE/0363) and local approvals from NRES Committee North West - Liverpool Central (12/NW/0678) and NRES Committee South Central - Oxford 12/SC/0508. Local NHS Research and Development approvals were received for all participating practices.

Study sponsor

The Medical Research Council (MRC) will carry out the role of sponsor, with MRC Human Nutrition Research (HNR) the lead unit, in accordance with the Research Governance Framework and will take on responsibility for securing the arrangements to initiate, manage and finance (subject to funding) the study, and to ensure any risks are identified and managed and that the research is of high quality. MRC HNR has been certified since January 2006 to the quality management standard ISO9001:2008 by Lloyds Register QA and is subject to twice yearly external audit.

Trial steering committee

The Trial Steering Committee (TSC) is chaired by Prof Martin Roland, Professor of Health Services Research in the University of Cambridge. Martin is Director of the National Primary Care Research and Development centre,

Special Advisor to RAND Europe and has been a practising GP for over 30 years. Other independent members include: Prof Nick Finan, who is Honorary Professor at UCL and Consultant Endocrinologist at University College London Hospitals and one of the leading UK specialists in obesity management who has been a co-author in numerous obesity-related trials; Dr Judith Dawson, a full-time GP and Locality Lead for GP Commissioning in Northampton; and two patient/public representatives, Mrs Norma Scullion and Mr Graham Rhodes. Ms Polly Page, Director of Operations for MRC HNR and chair of the unit Research Review Board is also a member of the TSC.

The study is not blinded and carries low risk with no rules for early termination, so it is felt that it is neither necessary nor appropriate to have a specific Data Monitoring and Ethics Committee in addition to the TSC.

Data handling and quality assurance

Participation will be under full informed consent, including for the storage and use of data collected. The Principal Investigator (PI) will be responsible for ensuring compliance with the Data Protection Act. Data collection forms will be kept in locked cabinets and an online database with secure encrypted transmission will be established by the database manager, accessible remotely by designated usernames and passwords and automatically backed up to ensure no loss of data. The PI and Trial Coordinator will monitor the accuracy of the database with validation checks against the data collection forms. All resulting datasets will be anonymised and stored securely.

Research dissemination and data preservation for sharing

The investigators will analyse data according to pre-defined analysis plans in a timely manner. For those analyses described in this proposal this will be within the lifetime of the grant. The PI shall ensure that the results of the trial will be submitted for publication in a peer reviewed journal, regardless of the outcome. Authorship of publications will be determined by ICMJE guidelines. As project partners, Weight Watchers understand that they will have no influence on the data analyses or publications, but they will be able to see publications 14 days prior to submission to check any factual information relating to the company. All scientific papers and reports are peer reviewed by the HNR Research Review Board and signed off before publication. A lay summary of the research findings will also be sent to participants and participating primary care practices at the end of the study.

MRC HNR will be custodians of the data resulting from the study and will ensure compliance with the Data Protection Act and the MRC policy for data sharing and preservation. The HNR database manager will take responsibility for data curation and archiving and all data sets will be kept securely with no access from

unauthorised personnel. Data will be stored so that it can be accessed, used and understood by subsequent users. When the investigators have completed their planned analyses, the anonymised data will be made available for use by others and will be shared under appropriate data sharing agreements. Primary data and the Trial Master File will be retained securely in their original form for a minimum of 10 years.

The commercial programme intervention will be delivered by an employee of company and the company will provide data on meeting attendance and website usage, but they will have no role in the study design, data analysis, data interpretation, or writing of the report.

Trial status

Ongoing. Recruitment was completed in February 2014.

Competing interests

ALA, SAJ, PA, and JCGH have received funding to their institutions from Weight Watchers and have given and received hospitality from providers of commercial weight loss services on a small number of occasions. PA and SAJ are conducting another publicly funded trial in which part of the intervention is delivered by and donated free by Slimming World and Rosemary Conley. Until January 2014, SAJ wrote a regular nutrition column for the Rosemary Conley Diet and Fitness magazine and received a fee. LC has received payment from Lighter Life Ltd for consultancy services. The other authors declare no conflicts of interest.

Authors' contributions

ALA is the Principal Investigator. ALA, SAJ, PA, JCGH, MS, and SC are grant holders. ALA and SAJ developed the research questions and designed the trial based on an original idea from SAJ. All authors contributed to the study design and development of the protocol. LC and AM provided statistical expertise in clinical trial design and AM will conduct the primary statistical analyses. MS and TM will lead the cost-effectiveness analyses outlined. SC will lead the qualitative workstream. AT is the Trial Coordinator. All authors have read and given final approval of the protocol.

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